THE HIGH COURT

[2023] IEHC 744
[2021 No. 1 PAP]
[2021 No. 3 PAP]
[2021 No. 4758 P]
[2021 No. 4759 P]

IN THE MATTER OF IRISH PATENT NUMBER EUROPEAN PATENT (IE) 1 427 415 "LACTAM-CONTAINING COMPOUNDS AND DERIVATIVES THEREOF AS FACTOR XA INHIBITORS" AND REGISTERED IN THE NAME OF BRISTOL-MYERS SQUIBB HOLDINGS IRELAND UNLIMITED COMPANY

– AND –

IN THE MATTER OF THE PATENTS ACT 1992 TO 2019

BETWEEN

BRISTOL MYERS SQUIBB HOLDINGS IRELAND UNLIMITED

PETITIONER

– AND –

NORTON (WATERFORD) LIMITED T/A TEVA PHARMACEUTICALS IRELAND

RESPONDENT

JUDGMENT of Mr Justice Max Barrett delivered on 8th December 2023.

SUMMARY

In this judgment I explain (i) why Irish Patent Number EP (IE) 1 427 415 is not valid, but (ii) how, by virtue of Delaware law, if it was valid (and it is not) it would enjoy its presently claimed priority date.

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(Stockholm, 2nd November 2022).

Appendix 20: Professor Morrissey's Oral Testimony in London

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CASES REFERRED TO IN THIS JUDGMENT

To avoid repeated case citations in the main body of this judgment and so to conserve space, the citations of various cases that are repeatedly referred to and/or considered in the main body of this judgment (not the appendices) are referred to below.

European Patent Office

Case G-0005/83 *(Second medical indication)* (ECLI:EP:BA:1984:G000583.19841205)
Case J-0019/87 *Assignee* (ECLI:EP:BA:1988:J001987.19880321)
Case G-0004/88 *Transfer of opposition* (ECLI:EP:BA:1989:G000488.19890424)
Case T-0939/92 *Triazoles/AGREVO* (ECLI:EP:BA:1995:T093992.19950912)
Case T-0590/98 *Radiopharmaceuticals/AMERSHAM PLC* (ECLI:EP:BA:2003:T059098.20030430)
Case T-1329/04 *(Factor-9/JOHN HOPKINS)* (ECLI:EP:BA:2005:T132904.20050628)
Case T-578/06 *Pancreatic cells/IPSEN* (ECLI:EP:BA:2011:T057806.20110629)
Case T-1642/07 (*Viral enhancement of cell killing/Arch Development Corporation*) (ECLI:EP:BA:2010:T164207.20101202)
Case T-0577/11 (*Entitlement to priority*) (ECLI:EP:BA:2016:T057711.20160414)
Case T-0205/14 *Ibandronate sodium, Form QQ/Teva* (ECLI:EP:BA:2015:T020514.20150618)
Case T-1201/14 *(Transfer of right of priority)* (ECLI:EP:BA:2017:T120114.20170209)
Case T-1103/15 *University of Alabama* (ECLI:EP:BA:2018:T110315.20180222)
Case T-1786/15 (*BMP Antagonists/General Hospital Corporation*) (ECLI:EP:BA:2020:T178615.20201015)
Case T-0488/16 *Dasatinib/BMS* (ECLI:EP:BA:2017:T048816.20170201)
Case T-1322/17 *Ibandronate/ATNAHS* (ECLI:EP:BA:2019:T132217.20190319)
Case G-0002/21 *(Insecticide compositions/Sumitomo*) (ECLI:EP:BA:2023:G000221.20230323)

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Teva Santé v. BMS Holdings Ireland Unlimited Company, Judicial Court of Paris, 8th June 2023.

Ireland

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Data Protection Commissioner v. Facebook Ireland Ltd [2019] IESC 46 [2019] 3 IR 255
Doyle v. Banville [2012] IESC 25 [2018] 1 IR 505.
Duffy v. McGee [2022] IECA 254
Glaxo Group Ltd & Patents Act 1992 [2009] IEHC 277
Keneally v. De Puy International Ltd [2016] IEHC 728 [2017] 2IR 487.
Kutchera v. Buckingham International Holdings Ltd [1988] I.R. 61.
Lehane v. Dunne [2018] IECA 7.
MacNamara v. Owners of the SS "Hatteras" (No. 2) [1933] IR 675.
McC v. McC [1994] 1 IR 293.
McCaughey v. IBRC [2013] IESC 17.
Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ltd v. Boehringer Ingelheim Pharma GmbH & Co. KG [2022] IECA 58.
O'Brien v. Clerk *of Dáil Eireann* [2016] 3 IR 384.
O'Callaghan v. O'Sullivan [1925] 1 IR 90.
O'Leary v. Mercy University Hospital Cork [2019] IESC 48.
Ranbaxy Laboratories Ltd v. Warner-Lambert Co [2007] IEHC 256.
Re Boehringer Ingelheim Pharma GmbH [2017] IEHC 495.
Unicredit Global Leasing Export GmbH v. Business Aviation Limited [2019] IEHC 139

[2019] 3 IR 689.
Walsh v. National Irish Bank Ltd [2013] IESC 2[2013] 1 IR 294.

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Advanced Bionics v. Med-El Elektromedizinische Geräte GmbH [2023] EWCA Civ 637.
Arrow Generics Ltd v. Merck & Co. Inc [2007] EWHC 1900 (Pat.).
Baron de Bode's Case (1845) 8 Q.B. 208, 115 E.R. 854.
Biogen Inc. v. Medeva plc [1997] RPC 1.
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HTC Corp v. Gemalto SA [2013] EWHC 1876 (Pat.).
Idenix Pharmaceuticals Inc. v. Gilead Sciences Inc. [2016] EWCA Civ. 1089.
KCI Licensing Inc. v. Smith & Nephew Plc [2010] EWHC 1487 (Pat.).
Kirin-Amgen Inc v. Hoechst Marion Roussel Ltd. [2005] RPC 9.
Medimmune v. Novartis [2011] EWHC 1669 (Pat.).
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Bausch & Lomb, Inc. v. Commissioner, 92 T.C. 525 (1989).
Beam Laser Systems, Inc. v. Cox Communications, Inc., 117 F.Supp.2d 515 (E.D. Va. 2000).
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Buechner v. Farbenfabriken Bayer AG, 38 Del Ch 490 154 A.2d 684, 686-87 (Del. 1959).
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*DePuy Inc. v. Zimmer Holdings Inc.*384 F. Supp. 2d 1237 (ND III. 2005).
Dickman v. Volmer 303 Wis. 2d 241, 736 N.W.2d 202 (Wis. Ct. App. 2007).
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Hollinger, Inc. v. Hollinger International, Inc., 858 A.2d 342, 347 (Del. Ch. 2004).
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Steelcase Inc v. Smart Technologies Inc. 336 F. Supp. 2d 714 WD Mich. 2004.
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Wallace v. Wood, 752 A.2d 1175, 1183 (Del. Ch. 1999).

VOLUME 1

I. SOME PREFATORY OBSERVATIONS

1

INTRODUCTION/SOME KEY POINTS

1. Structure of Judgment

1. This case has involved a quite enormous amount of evidence. In order that all of that evidence might properly be considered and in order that the issues arising between the parties might appropriately be analysed, I have broken the judgment into various parts and chapters so that there is a coherency to how it proceeds. Thus:

- Part I ("*Some Prefatory Observations*") touches on some issues that it seems to me might usefully be addressed so as to give the reader a flavour of what is to come in later parts so that her reading of the judgment is more informed from the outset.

- Part II ("*The Opening Submissions*") considers the opening submissions of both sides, a process that I found useful, in a case which presents with many issues, in identifying what issues and controversies each party considered important and how they respectively considered that they ought to be resolved.

- Part III ("*The In-House Evidence*") considers what I have loosely styled as the 'in house' evidence that was put/heard before me, namely the evidence of Mr Brown, Ms Leung, and Mr Golian.

- Part IV ("*The Evidence of Messrs Rasser and Granwell*") considers the evidence of Messrs Rasser and Granwell.

- Part V ("*The EPC-Related Evidence*") considers evidence and issues related to the European Patent Convention.

- Part VI ("*The Evidence as to United States Federal Law*") considers evidence and issues related to the application of United States federal law to the priority issue presenting.

- Part VII ("*The Evidence as to Delaware Law*") considers evidence and issues related to the application of Delaware law to the priority issue presenting.

- Part VIII ("*The Scientific Evidence*") makes some prefatory observations as regards the scientific evidence that follows.

- Parts IX –XI consider respectively the pharmacology evidence (Part IX), the pharmacokinetic evidence (Part X), and the medicinal chemistry evidence (Part XI).

- Part XII – XIV considers issues of judicial comity (chapter 30) and some concerns raised as to the expert evidence in this case (chapter 31), and the consolidated cases G1/22 and G2/22 (chapter 32), before reaching certain final conclusions (chapter 33).

2. Most parts begin with a chapter that makes certain prefatory observations, to some extent setting the scene for the consideration of the evidence that follows. There are also various chapters (typically headed "*Some Conclusions*") in which I seek to draw together various conclusions from the evidence just considered.

3. Each chapter contains numerous headings and sub-headings. Those headings and sub-headings are signposts to what is considered in the ensuing paragraph/s. They do not seek comprehensively to describe what follows beneath the relevant heading and should not therefore be used in the interpretation of this judgment.

4. There are also numerous appendices to the judgment. Appendices 1-16 contain witness statements that have been provided to me, which I have abridged, to which the chapters occasionally cross-refer, and without which the consideration of the extensive evidence before me cannot properly be understood. Obviously, in arriving at the conclusions that I have reached in this judgment, I have had regard to the entirety of the evidence before me in its complete form.

5. Appendices 17-19 contain English-language versions of the judgments obtained in the parallel proceedings in France, Norway, and Sweden. They have been included (i) so that the chapter and commentary on judicial comity might better be understood, and (ii) because English-language versions of those judgments are not generally available.

2. Two Plinths to the Present Proceedings

6. There are two key plinths to the within application.

7. First, Teva has attacked the priority claimed for Patent No. EP(IE) 1 427 415 (the 'impugned patent'). The attack is based on the contention that the wrong BMS[1] company applied for the impugned patent. More particularly, Teva maintains that BMS Co., the applicant for the international application that designated the European patent from which the impugned patent emerged, could not claim priority because the rights in the priority document (US165) had been assigned to BMS Pharma Co, *i.e.* not BMS Co. BMS's case is that BMS Co. was entitled to invoke priority from US165 because it was the beneficial owner of it.

8. When it comes to the first plinth, my attentions have been drawn to the observations of Birss J., as he then was, in *Accord Healthcare Ltd v. Research Corporation Technologies* [2017] EWHC 2711 (Pat.). That was an action concerned with the validity of European Patent (UK) No. 0,888,289 which covered an anti-epileptic drug called 'lacosamide'. The patent arose out of work which had been carried out at the University of Houston by a Professor Kohn and his group since the 1980s. Although the patent had expired in March 2017, a supplementary protection certificate provided on-going protection for lacosamide until 2022. The defendant (RCT) was the proprietor of the patent and its exclusive licensee sold lacosamide for use in the treatment of epilepsy. A percentage of the licence fees paid to RCT in respect of lacosamide went back to the University of Houston and to Professor Kohn and his group. Accord, as claimant, contended that the patent was not entitled to the priority date claimed, namely 15th March 1996. RCT accepted that, if priority was lost, the patent was invalid in the light of a paper referred to as Choi. If the patent was invalid, the supplementary protection certificate would be revoked leaving the path clear for generic competition. Accord also contended that the patent was invalid on grounds of obviousness in any event. It appears not to have been in dispute in the case that (i) the inventor of lacosamide was Professor Kohn and (ii) he had assigned his right to claim priority to RCT by an assignment in writing dated 4th February 1997.

[1] The applicant for the patent was Bristol Myers Squibb Company (generally referred to in this judgment as 'BMS Co.'). Its successor in title was Bristol-Myers Squibb Pharma Company (generally referred to in this judgment as 'BMS Pharma'). Instead of using the words "*Bristol-Myers Squibb*" repeatedly in this judgment, I have generally used the acronym 'BMS'. When quoting from texts I have also typically shortened "*Bristol-Myers Squibb*" to 'BMS' within the quote. This has yielded a general consistency of terminology that should assist in the reading of the judgment.

The international patent application which resulted in the grant of the patent covering lacosamide had been filed on 17th March 1997. The question of entitlement accordingly had to be assessed as at that date. It was Accord's case that the assignment only took effect as an assignment of bare legal title to the invention and the priority claim and that this was insufficient. Accord argued that equitable or beneficial title to that property remained with the University of Houston as 17th March 1997 and that this was not something that could be corrected retrospectively. In the course of his judgment in *Accord*, Birss J. observes as follows, at §77:

> "*I cannot help but observe that if priority is lost this patent would be revoked over a publication by the inventor in the period between the priority date and the filing date which I infer was assumed to be a safe thing to do because it was assumed by everyone involved that priority would be successfully claimed. There will be many cases like this. There is no obvious public interest in striking down patents on this ground, unlike all the other grounds of invalidity'*."

9. Priority would fall to be lost in the same way in this case. So the cautious note struck by Birss L.J. is noteworthy.

10. It became apparent during the process of examination and cross-examination in these proceedings that there is a significant measure of agreement between the expert witnesses on Delaware law, Messrs. Steele and Chandler, as to the principles of Delaware law and the operation thereof as between BMS Co and BMS Pharma in respect of US165. Most significantly, both essentially agree – I call this the '**Common Delaware Evidence**' – that BMS Co is the equitable owner of US165 under Delaware law.[2] This in a case where, in essence, BMS has canvassed for the proposition (hereafter I call this the '**Control Proposition**') that (i) ownership of a subsidiary, coupled perhaps with parent company policies which embrace that subsidiary, along with the fact that (ii) Delaware law recognises that, as between a parent company and its subsidiary, the latter (including its officers) owes fiduciary duties to the former suffices to render the Delaware parent company in this case (BMS Co.) the equitable owner of the intellectual property assets of its subsidiary (BMS Pharma). Critically, when it comes to the Control Proposition, I am not viewing matters through an Irish-law perspective but from a Delaware law perspective, and when it comes to Delaware law I am confronted with the Common Delaware Evidence. So it seems to me that (i) I must acknowledge and have regard to the equitable ownership that Delaware law would recognise when conducting my analysis, and (ii) I cannot, in the face of the Common Delaware Evidence accept any invitation from Teva to reject that equitable ownership or to disregard its existence. Because, repeatedly in the text that follows, I will need to make again the observations that I have made in this paragraph, I shall avoid repeating those observations and simply refer to them as the 'Paragraph 10 Point'.

11. The second plinth of Teva's application has involved it making sufficiency and obviousness attacks on the impugned patent. These combined attacks raise essentially the same issue, namely that of plausibility, *i.e.* whether the description of the application for Patent WO652, when read in the light of the common general knowledge (CGK) at the priority date about factor Xa inhibitors renders apixaban – Example 18 in the patent application – plausible as a factor Xa inhibitor.

12. Plausibility, I note, is not a statutory requirement. It is a concept which has been judicially developed to prevent speculative claiming. Up to the decision of the EPO's Enlarged Board of Appeal in Case G2/21 *Sumitomo*, the Irish and English courts have held that if a claimed invention is not plausible, there can have been no technical contribution with the consequence that the claimed invention lacks inventive step and/or the patent is insufficient.

[2] Mr Steele, the expert witness on Delaware law called by Teva, expressed some reservation as to whether some supervening additional requirement applied under the US Patents Act (a federal measure) could offset what would otherwise be the effect of Delaware law to confer equitable ownership of US 165 on BMS Co. However, the evidence before me shows there to be no such supervening additional requirement.

13. In Case G2/21 the Technical Board of Appeal referred questions on the principle of free evaluation of evidence and the notion of 'plausibility' in the context of inventive step to the Enlarged Board of Appeal. The core dispute in that case concerned European patent EP 2 484 209 regarding an insecticide composition. According to the patent, two compounds known for their insecticidal effect had a synergistic effect when mixed. In dealing with the issue of plausibility the Enlarged Board of Appeal considered that that concept did not amount to a distinctive legal concept or a specific patent law requirement, but rather was a "*generic catchword*". (This avoided the difficult issue of whether technical effect is a matter of *ab initio* plausibility or implausibility.)According to the Enlarged Board, the relevant standard for reliance on the purported technical effect when assessing whether or not claimed subject matter involves an inventive step is what the skilled person, with CGK in mind, would understand at the filing date from the application as originally filed.

14. Although I have said that Teva has made sufficiency *and* obviousness attacks, in fact the case has largely focused on sufficiency. The written closing submissions of BMS state why this is so in terms which I respectfully adopt:

> "*It is said that 652 does not plausibly disclose that apixaban is a factor Xa inhibitor and that it is accordingly insufficient within the meaning of section 58(b) of the Patents Act 1992. It is also said that the claims of the Patent contain no technical advance over the disclosure of WO 00/39131 for the same reason and accordingly that they lack inventive step/are obvious. The allegation of obviousness adds nothing to the case: it is common ground that 131 only encompasses apixaban as part of its Markush formulae and does not disclose a compound with a lactam in the P4 position at all. Consequently, 131 does not disclose apixaban in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. It follows that, if the court determines that 652 also does not render apixaban plausible as having factor Xa inhibitory activity, then the Patent is invalid for insufficiency and obviousness. Conversely, if the court determines that 652 does render apixaban plausible as having factor Xa inhibitory activity, then 652 is sufficient and is not obvious over 131. Consequently...the only question the court has to answer is whether 652 makes apixaban plausible as a factor Xa inhibitor.*"

3. Other Jurisdictions (Comity)

15. I address the issue of judicial comity at some length in chapter 30. However, it seems appropriate that I also make some introductory observations here. This section should be read in conjunction with chapter 30 and *vice versa*.

16. Ireland is neither the first nor the only jurisdiction in which the validity of the impugned patent has been challenged. Teva has been unsuccessful in several jurisdictions to this time, with the notable exception of the United Kingdom. Thus, Teva has failed in France, Norway, and Sweden, all sister signatories to the European Patent Convention.

17. Unsurprisingly, Teva has sought to focus my attentions on the reasoning of the English courts in *Sandoz Ltd v. BMS Holdings Ireland Unlimited Co.* [2022] EWHC 822 (Pat.) (as affirmed on appeal in [2023] EWCA Civ. 472).

18. For obvious reasons, weight and respect falls to be accorded by me to the decisions of the neighbouring jurisdiction, largely because the courts of that jurisdiction are applying the same system of patent law and both are common law jurisdictions. That said, I have an obligation to decide the case before me on the evidence presented to me and not on the evidence presented to any other court, whether in the United Kingdom or elsewhere. If the evidence is different, then the outcome may be different. The position in this case is, therefore, different from that which

presented, *e.g.*, in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ltd v. Boehringer Ingelheim Pharma GmbH & Co. KG* [2022] IECA 58. There, the issues were being litigated with evidence from the same experts in multiple jurisdictions. By contrast, where (as here) different experts give evidence it may well be that upon due consideration, a court will conclude that the relevant facts should be differently determined because the evidence is different.

In fact, as will be seen in chapter 30, this aspect of matters has proven easier to resolve than I initially anticipated. This is because the French, Norwegian, and Swedish judgments can be distinguished fairly readily, leaving the English judgment as 'the last man standing'. The priority point was not argued in the United Kingdom, and my conclusion as to plausibility/validity is the same as the United Kingdom courts, so there is not just comity, but accord in this regard. There was discussion before me as to whether the evidence before me was entirely similar to the evidence which went before the London court. I do not know if it was and I do not know that the point needs to be explored in any detail in circumstances where my judgment accords in any event with that of the United Kingdom courts on plausibility/validity. I have decided this case on the evidence before me and I take comfort in the fact that (i) my judgment chimes with that of the United Kingdom courts in terms of plausibility, and (ii) the discordant French, Norwegian, and Swedish judgments can be distinguished fairly readily.

4. Typographical Errors and Commercially Sensitive Information

19. As with the previous judgments that I have given in these proceedings, I will give the parties a few weeks from the date of issuance of this judgment to read it. Thereafter, they might kindly let me know if they consider that (i) the judgment contains any obvious typographical errors that require correction, and (ii) I have mentioned commercially sensitive information which ought not to be included in the publicly obtainable version of this judgment. (As to (ii), I will decide, if and after any such information is flagged to me whether or not it merits exclusion.) I would suggest that the parties revert to me by 15th January next.

II. THE OPENING SUBMISSIONS

2

The Opening Submissions for Teva and BMS

A. Introduction

20. I found the opening submissions of both sides to be helpful in terms of indicating the key issues that BMS and Teva respectively consider to be of significance and proceed now to consider some elements of those opening submissions.

B. The Opening Submissions for Teva

1. Priority

21. Teva opened its case by observing that there are two key issues now before me, namely the priority issue and the validity/plausibility issue. The priority issue concerns the validity of the Irish patent (Patent 415) and the associated supplementary protection certificate. When it comes to priority there is a helpful diagram included in the *Book of Opening Submissions for the Petitioner* which might usefully be replicated in a slightly different form at this juncture so as to understand better all the points made concerning priority in the pages that follow:

21/09/2001.	US165 filed in the names of the inventors, Drs Pinto and Quan.
02/10/2001.	Change of name of DuPont to BMS Pharma.
3/11/2001.	Assignment of Pinto and Quan rights to BMS Pharma.
17/09/2002.	Application WO 03/026652652 filed by BMS Co, entitled 'Lactam-Containing Compounds and Derivatives thereof as Factor Xa Inhibitors' '
23/04/2007.	Assignment of rights by BMS Pharma to BMS Co.
13/12/2016.	Assignment of rights by BMS Pharma to BMS Co.

22. The impugned patent has a priority date of 21st September 2001. However, it is disputed between the parties that this is the priority date. The invention at issue in this case relates to lactam-containing compounds and derivatives thereof (factor Xa inhibitors). Teva maintains that the right of priority arising from US165 was not assigned from the inventors and the original applicants for the United States patent to BMS Co. prior to the filing date. Teva maintains that this is fatal to the claimed priority date.

23. Teva maintains that as of the filing date BMS Co. was not the owner of US165 and, accordingly, BMS Co. cannot claim priority from US165 and, as BMS Co. is not entitled to claim priority, the claims of the patent do not describe a patentable invention, as it was not new (having regard to the matter which formed part of the state of the art as of the filing date). In this regard, the petitioner relies on the matter contained in W0681, with a priority date of 10th September 2001.

24. It is common case that the priority challenge is resisted solely on the basis of beneficial ownership. Teva believes that the notion of beneficial ownership is a retrospective attempt to create beneficial ownership in BMS Company when (per Teva) it does not have such ownership.

25. The BMS defence makes a number of admissions. There is an admission that the patent claims priority from the filing of US165. (That filing was in the names of the inventors, Drs Pinto and Quan). It is admitted that ER Squibb and Sons LLC and BMS Pharma Holding LLC acquired DuPont Pharmaceuticals on 1st October 2001 and the acquired company thereafter changed its name to BMS Pharma. It is admitted that Drs Pinto and Quan, subsequent to the purchase, entered into an assignment dated 3rd November 2001 with BMS Pharma. It is admitted that on 17th September 2002

Application 652 was filed, by BMS and it is admitted that BMS Pharma entered into an assignment dated 23rd April 2007 and a further assignment dated 13th December 2016 to BMS Company. Those postdated the filing date.

2. The European Patent Convention

26. Counsel for Teva turned next to the substance and operation of the European Patent Convention when it comes to priority rights. I consider the European Patent Convention aspects of these proceedings after I outline, later below, the evidence of Dr Kinkeldey and Mr Rennie-Smith, the expert witnesses called to give evidence on the Convention and its operation.

3. The First Statement of Mr Golian – Part 1

27. Counsel turned next to the first statement of Mr Golian, a vice president and an assistant general counsel of BMS who was called by BMS to give evidence in these proceedings. An abridged version of his written evidence is set out at Appendix 5. Mr Golian's evidence is considered in some detail later below so I do not pause to consider it in detail here. For now I simply note that Mr Golian avers, amongst other matters, as follows:

> "*5. From the commencement of my employment with BMS on 1st July 2002, my experience has been that decisions as to how intellectual property assets are to be held have been made by BMS Company for both it and its wholly owned subsidiaries. Typically, these decisions are made by BMS Co's intellectual property lawyers, often in consultation with BMS Co's tax department and other areas of BMS Co's legal department. When I was working for BMS Co in Wilmington, for instance, BMS Pharma did not have its own independent intellectual property lawyers or legal department. I have personally been involved in many such decisions regarding the holding of intellectual property that have been made by BMS Co over the years as part of my role as intellectual property attorney at BMS Co since 1 July 2002.*
>
> *6. As far as I am aware, prior to my arrival it has always been the case that BMS Co has made the decisions as to how it and its wholly owned subsidiaries hold their intellectual property assets, including prior to its acquisition of the DuPont pharmaceuticals business.*
>
> *7. This appears to me to be borne out by emails dated 19th October 2001 and 29th October 2001, which I have been shown and which are attached to this statement as appendix [PG1] and [PG2] respectively*" –

28. The emails to which Mr Golian refers are of some importance in this case and it is worth breaking my outline of the opening submissions made by counsel for Teva and engaging in a brief aside on the emails to which Mr Golian refers in the just-quoted text.

4. An Aside on the Emails of October 2001

29. As I just mentioned, the emails of 19th and 29th October 2001 are of some importance in this case. The email of 19th October 2001 reads as follows:

> "*Subject: Re: Thanks and reminder*
> *Date: Fri, 19 Oct 2001 15:09:50-04:00*
> *From: Robert Souka…*
> *Organization: BMS*
> *To: Francis S Rossi*
>
> *Frank*
>
> *I have delayed a bit since the total situation is still a little fluid…this is the current domestic status of the DuPont businesses that I am aware of:*

Bristol Myers-Squibb Pharma Research Labs, Inc
This is the old DPRL entity that conducts contract research (compound screening services) for BMS Pharma Company (old DPC) under a cost plus arrangement. This entity owns some intangibles and leases space in San Diego and San Francisco, California. The employees of this entity are carried on the books of BMS Pharma Company but charged to BMS Pharma Research Labs under a service agreement (leased employees). This entity is 100 %owned by ER Squibb and Sons LLC.

Bristol-Myers Squibb Medical Imaging Inc
This is the old DCII entity that previously only contained the Definity patents. Effective at closing, this entity is to house the Billerica (imaging business) operations and business. The Billerica personal property was purchased from DuPont Parent (E.I. Dupont de Nemours) by ER Squibb & Sons LLC (ERS) and was subsequently contributed to BMS Medical Imaging. ERS owns 100% of the stock of BMS Medical Imaging. Billerica payroll is currently reported under Bristol-Myers Squibb Pharma Company (old DPC) due to a payroll systems constraint but is being charged to BMS Medical Imaging on a management basis. Effective 11/1, the Billerica employees will be formally transferred on the payroll system to BMS Medical Imaging. The Billerica real estate (land and buildings) is owned by old DPC but is being leased to BMS Medical Imaging. Some intangibles of the Imaging business appear to be on DPC's books…we are still deciding if they are to be transferred to BMS Medical Imaging or licensed to them. Accordingly, BMS Medical Imaging is both the manufacturer and owned of the Imaging business.

Bristol-Myers Squibb Pharma Company
This is a Delaware partnership currently owned 50% by ER Squibb & Sons LLC and 50% by Bristol-Myers Squibb Pharma Holding Company LLC (BMS Pharma Holding entity is 100% owned by ERS – but the ownership is subject to change). BMS Pharma Company houses most of the intangibles, the acquired sites and realty (Billerica, Garden City, Experimental Station, etc) and pharmaceutical operations formerly operated by DuPont. This company leases employees to BMS Pharma Research Labs and realty to BMS Medical imaging.

Bristol-Myers Squibb Finance Company
While this entity (100% owned by BMS Company) is not really part of the DuPont transaction, I felt you should be aware of its existence. BMS Finance Company was established to be a venture capital bank for all future business ventures and acquisitions. This entity loaned the funds to ERS and BMS Pharma Holding for their purchase of the DuPont businesses and other ventures (ImClone, etc)

Hopefully, this helps. Let me know if you need more details.

Bob"

30. The email of 29th October 2001 is very brief; its true significance is that it is written over the head of a more substantive email of 24th October 2001.

"*Subject: [Fwd: Legal Ownership of Patents & Trade marks – Danube]*
Date: Mon, 29 Oct 2001 08:16:19-0500
From: Mark S. Sobecki
Organization: Bristol Myers-Squibb
To: Cory Zwerling…Alan R Bauer…Marla J Mathias…David T Bonk…Nadine P Flynn…Sandra Leung
Cc: Raymond T Keane…Frances S Rossi…Margaret Yonco-Haines

All

Please note the attached. If there are any issues of concern about these alignments, please let Margaret Yonco-Haines know.

Subject: Re: Legal Ownership of Patents & Trademarks – Danube
Date: Wed, 24 Oct 2001 08:53:05-0400
From: Frances: S Rossi…
Organization: Bristol-Myers Squibb
To: Margaret Yonco-Haines…
Cc: Sobecki Mark….

Margaret – I am copying Mark Sobecki with your message as he is integration counsel for the Diagnostics business. fsr

Margaret Yonco-Haines wrote:

We have determined the following 3 categories of 'DuPont Pharma' patents and trademarks, based on the business to which the intangibles relate. Please let us know if any of our recommendations for legal entity registration of these intangibles doesn't make sense from your perspective (I include the cc's in that request) –

(1) Patents and trademarks related to the pharmaceutical business. – Maintain legal ownership in Bristol-Myers Squibb Pharma Company (formerly DPC). We believe that this is the entity where they currently reside, so this should only involve a name-change. New patents and trademarks in the name of Bristol-Myers Squibb Company.

(2) Patents and trademarks related to the radiopharm business – Retain Definity in Bristol-Myers Medical Imaging, Inc (formerly DuPont Contrast Imaging, Inc). Transfer all other patents and trademarks relating to the radiopharm business (believe they are currently held in BMSPC) to BMMII.

(3) Patents and trademarks related to the CombiChem (DPRL) business. This business is expected to be sold very soon, therefore all trademarks and patents related to the business – to the extent they will be included in the sale – should be assigned to the entity , Bristol-Myers Squibb Pharma Research Labs, Inc (formerly DuPont Pharmaceutical Research Labs, Inc. and before that, Combi Chem). Apparently at least some of the intangibles are still registered in the name of Combichem – and it is my understanding from representations DuPont tax made in due diligence that DPRL is the same legal entity as Combichem. I spoke with Doug Worthington, who is the legal counsel working on this disposition, and he indicated that decisions are being made regarding which patents and other intangibles are going to be sold with the business, since we may retain some – so any transfers should be coordinated with him. Any intangibles not transferred with the business should stay at BMSPC.

Margaret"

5. The First Statement of Mr Golian – Part 2

31. Returning to Mr Golian's statement, he moves on to aver, amongst other matters, as follows:

"*11. The 24th October 2001 email reflects decision making by BMS Co as to the legal ownership of Bristol-Myers Squibb Pharma Company's intellectual property, and the putting in place* [of] *a* ***policy*** *in that regard, consistent with my experience of BMS Co being the decision maker and having control over how the intellectual property assets of its wholly owned subsidiaries are to be held .* [My emphasis].
12. The same ***policy*** *described in the email, whereby legal ownership of Bristol Myers-Squibb Pharma Company's pharma IP assets remained with that entity, and only required a name change from DuPont Pharmaceuticals Company to Bristol Myers-Squibb Pharma Company, was in place when I joined BMS Co on 1 July 2002. I was aware of that* ***policy*** *and recall being involved in the preparation and filing of paperwork to effect such name changes around the time I began in BMS Co. Effecting name changes was less costly and time-consuming than it would have been to have Bristol-Myers Squibb Pharma Company assign all those rights to BMS Co, so there were practical benefits to that approach in circumstances where – in my experience and as appears from the October 2001 emails – BMS Co in any event had control over the ownership of those intellectual property assets such that it could have been decided to have Bristol-Myers Squibb Pharma Company assign those intellectual property assets to it at a later date as and when required.*"

[Emphasis added]

32. I have emphasised the word 'policy' in the above-quoted text. This is because Teva, on account of the Control Proposition, spent no little time in these proceedings on the 'issue' as to whether or not the above emails and/or an in-house BMS manual constituted a policy and whether or not that policy had been implemented within BMS. However, I would respectfully refer the parties to the Paragraph 10 Point in this regard.

6. The Observations of Ms Marla Mathias

33. Counsel for Teva turned next in his opening remarks to a statement by Ms Marla Mathias, a former vice-president and chief patent counsel of BMS. This statement stands in an unusual position in these proceedings in that the statement itself is not in evidence before the court and yet the statement is referred to by various of the parties in statements that are in evidence before the court. It is an appendix to the first statement of Mr Chandler, an abridged version of which appears in Appendix 1 hereto. Rather than re-quote that statement, I would respectfully refer the reader to that Appendix and confine myself hereafter to certain observations that counsel for Teva made in relation thereto (and certain observations that I have made regarding those observations):

(i) Teva: Ms Mathias states, amongst other matters, that she "*met with patent attorneys at DuPont [Pharmaceuticals Company], including those who would join BMS after the closing. I also attended meetings* [with]*…our external lawyers…to discuss issues such as which entity should hold, and which should have a licence to, those patents that were of interest to both BMS and E.I. Du Pont de Nemours and Company*." So the concept of which company should hold what was clearly treated as a matter of some seriousness, sufficiently serious to demand the direct involvement of Ms Mathias, a senior company officer.

Comment: This aspect of the case falls to be decided by reference to Delaware law. In this regard I am confronted with the Common Delaware Evidence, and so again I would make the Paragraph 10 Point in this regard.

(ii) Teva: Teva has drawn my attention to the fact that Ms Mathias states, amongst other matters, as follows:

> "*After the closing, one of the main activities that I undertook was to supervise the integration of the patent docketing and renewals arrangements of what was by then BMS Pharma….We did not take any steps to transfer legal title to the patents and patent applications held by what was by then BMS Pharma Company to BMS. It was a no-brainer to leave them where they were as we had access to them anyway so why go to the effort of assigning them? There was no need to transfer legal title, and it would have made no sense to do so, as BMS was able in effect to treat BMS Pharma as a bucket out of which the intellectual property rights which it held at the closing could be withdrawn as necessary or otherwise deployed.*"

Despite it apparently being a "*no-brainer*" to leave the assets where they were, they were in fact subsequently assigned to BMS Company by way of the assignments of 23/04/2007 and 13/12/2016.

Comment: To examine the 2007 and 2016 assignments (including the efforts to parse them that I consider later below) seems to me to be (following on the evidence that I heard at the proceedings) a distraction. This is because, as a result of the Common Delaware Evidence, the most that can have been transferred in the assignments of 2007 and 2016 was BMS Pharma's legal interest. Thus, it seems to me to get one nowhere in the circumstances presenting to consider the wording of the assignments of 2007 and 2016 in any detail; however, as the point has been raised I examine it later below. The same point falls to be made as regards (i) Ms Mathias's statement that "*There was no need to transfer legal title, and it would have made no sense*

to do so, as BMS was able in effect to treat BMS Pharma as a bucket out of which the intellectual property rights which it held on the closing could be withdrawn as necessary or otherwise deployed".

(iii) Teva: Teva has drawn my attention to the fact that Ms Mathias states, amongst other matters, as follows:

> "*Another way of describing how BMS Pharma was seen as holding such intellectual property is set out in an email of 19th October 2001 from Robert Souka to Francis Rossi* [considered previously above in this judgment]….*This states that BMS Pharma… houses most of the intangibles, the acquired sites and realty…and pharmaceutical operations formerly operated by DuPont*",

and that Mr Golian averred in his first statement (considered previously above) that

> "*The 24th October email forwarded by* [Mr] *Mark Sobecki sets out a series of recommendations regarding 'legal ownership of patents and trademarks' in connection with the DuPont acquisition*",

and that this suggests that what was at play was not any immutable or fixed policy but merely "*a series of recommendations regarding 'legal ownership of patents and trademarks' in connection with the DuPont acquisition*".

Comment: In this regard I am confronted with the Common Delaware Evidence, and so again I would make the Paragraph 10 Point in this regard.

(iv) Teva: Teva has drawn my attention to the fact that Ms Mathias states, amongst other matters, as follows:

> "*My recollection of how we dealt with the intellectual property rights which BMS Pharma…held as at the closing is also confirmed by an email…by Mark Sobecki on October 29 2001* [as considered previously above in this judgment]….*I am pretty sure that not only would I have been involved in the discussions which led to these decisions, but that this email was memorializing decisions and planning that had been underway since June….For the reasons I have given above, leaving everything related to the pharmaceutical business in BMS Pharma…was not a memorable decision, and had surely been the default one from nearly the beginning of our due diligence. I can't think of any reason why one would have done it any other way…*",

Comment: Again, this aspect of the case falls to be decided by reference to Delaware law. In this regard I am confronted with the Common Delaware Evidence, and so again I would make the Paragraph 10 Point in this regard.

7. The Witness Statement of Ms Sandra Leung

34. Counsel for Teva led me next to a witness statement sworn by Ms Sandra Leung who started out as a staff attorney in 1992 and is now an executive vice president and the general counsel of

BMS Company, so clearly an individual of standing and distinction. That witness statement is set out in Appendix 8. Ms Leung gave oral evidence in this case and I consider her evidence and that of Mr Brown and Mr Golian later below, so I do not pause to consider her evidence at length here.

35. Counsel for Teva, in the course of Teva's opening submissions, appeared to attach some significance to the fact that Ms Leung, whose witness statement is dated 3rd August 2022, was the first of BMS's internal witnesses to mention the concepts of legal and beneficial ownership. That may be so but as I show later in this chapter the Control Proposition has repeatedly been put forward by BMS since January 2022.

8. Some Perceived Difficulties as Regards the Interrogatories

36. Counsel for Teva turned next to a couple of perceived difficulties with some of the interrogatories in this case. Of note in this regard are the perceived difficulties that have arisen with Interrogatory 5.17, which (with the answers given) I replicate below:

"*5.17*	*Did not BMS Company lay out the policy as to how patents were to be held as between BMS Company and BMS Pharma?*
Answer:	*More precisely, it laid out the policy as to 'legal entity registration' of patents from the acquired DuPont pharmaceutical business which was to 'maintain legal ownership in BMS Pharma' in respect of existing rights already residing there and to put new patents and trade marks in the name of BMS Company.*
Response:	*Insufficient reply. If 'it' is intended as a reference to the email of 24th October 2001, does not that email concern a 'recommendation' by the tax department of BMS Company and not a decided policy of any entity? Is it not erroneous to state that the email of 24th October 2001 contains a single policy or recommendation "…as to 'legal entity registration' of patents from the acquired DuPont pharmaceutical business'? Rather, is it not the case that there was a recommendation for different treatment of different categories of 'Du Pont Pharma' patents and trademarks?*
Further Answer:	*BMS Co controlled how the intellectual property acquired in the DuPont acquisition should be held and dealt with. The email of 24th October 2001 is evidence of part of that process whereby the proposed policy at that point, just after acquisition, as to how the rights were to be held was circulated and comment invited. The implementation of the policy is the province of oral evidence to be given at trial.*"

37. A couple of points might usefully be made by me in this regard:

(i) I do not see anything in the just-quoted series of exchanges beyond the usual to-ing and fro-ing that one gets in interrogatories and further interrogatories. The final answer shows that BMS is holding firm to the Control Proposition (leading one again to the Paragraph 10 Point).

(ii) Ms Leung suggests in her written statement that the email of 24th October 2001 was consistent with an already extant general policy. Yet whoever drafted the answer to the interrogatory suggests that the email was part of the formulation of a proposed policy. So was the policy extant or being formulated or was there a policy at all? In a case with thousands of pages of evidence, coupled with oral testimony, I suspect it is always going to be possible to engage in a parsing exercise that yields some level of ostensible

inconsistency. I do not know the answer to the question that I have just posed but neither does it seem to me especially to matter in circumstances where the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point.

38. There is also another interrogatory, Interrogatory 4 ("*Assignments*"). It states as follows:

> "*4.1* *Arising from the Assignment dated 23rd April 2007 between BMS Pharma and BMS Company:*
>
> *4.1.1* *As of 23rd April 2007, did not BMS Pharma own the entire right, title and interest in all countries of the world in and to the application for US165?*
>
> *Answer:* *This question raises a question of law, as distinct from information/admissions of fact relating to the facts in dispute is not a proper matter for interrogatories.*
>
> [Counsel for Teva suggested that this answer is wrong, that the basis for my ownership of the property is a question of law but whether I own it or not is a question of fact. I am not persuaded that that is correct. It seems to me that I may claim to own something in fact but whether I do own it or not is fundamentally a question of law. I may tell someone that I own my house but whether I truly and fully do would be down to a consideration of, *e.g.*, the chain of title and, *e.g.*, any (if any) related mortgage documentation.]
>
> *4.1.2* *Did not BMS Pharma assign to the BMS Company the entire right, title and interest in all countries of the world in and to the application for US165?*
>
> *Answer:* *Without prejudice to the question of the legal effects of its contents, BMS Pharma did execute such a form of assignment, with references to the right to claim priority and consideration referred to in paragraphs 4.1.3 and 4.1.4.*
>
> *4.1.3* *Did not BMS Pharma assign to BMS Company the right to claim priority from the application for US 165?*
>
> *Answer:* *Please see the answer to 4.1.2.*

39. Teva has complained of the uninformative circularity of the answers to Questions 4.1.2 and 4.1.3. I am afraid that I do not see the answers to be uninformative or circular. BMS answers as to matters of fact. It does not speak in its answers to matters of law.

9. The BMS Emails of 2002 – Part 1

40. In addition to the trio of emails from October 2001, I was referred to a number of intra-BMS emails from 2002. The first of these was sent on 30th January 2002 and is in reply to an undated preceding email. The emails read as follows:

> "*To: Lori B. Allaire…*
> *Cc: Diane Bartram… Marla Castlado…Bierlein Denise M…Collins, Cathleen M…Pickering Diane C…Scott Larsen…Dolan PhD. Peter…Jing Belfield…Vanatten Mary…*
> *From: Blair Q. Ferguson…*
> *Sent: 1/30/2002 10:06:50 PM (UTC)*
> *Subject: Re Bristol Myers v. Bristol Myers Pharma*
>
> *Thanks, Lori. Below is the guideline we should follow.*

All DuPont Pharmaceutical Company (DPC) cases which claim priority to a filing date prior to 10/1/01 [the author uses American dating style throughout his email] *should be in the name of…BMS Pharma….Thus, if the provisional is filed prior to 10/1/01, all subsequent filings worldwide claiming this priority should be in the name of BMS Pharma. BMS Pharma is a Delaware general partnership. For all Wilmington cases having an earliest priority date after 10/1/01, the name of* [the] *assignee should be…BMS.*

As you know, Denise is handling the recording of the name change worldwide. Going forward we all need to check on this for each case to make sure we have the right name of the assignee in assignments and other documents for the case.

There are 2 other DPC-related entities you should be aware of. The former CombiChem patent estate (currently being divested) is in the name of BMS Pharma Research Labs, Inc. The prosecution and maintenance of this estate is being handled by Townsend and Townsend and Crew. The former ImaRx patent estate is in the name of BMS Medical Imaging, Inc. The prosecution and maintenance of this estate is being handled by Woodcock Washburn. These cases have not been tracked in CPI or Memotech.

Please call if you have any questions.

Thanks.

Lori B. Allaire wrote:

Blair,

On my visit to Wilmington, Denise advised that cases filed prior to 10/1/01 would be in the name of BMS Pharma Company and for cases after 10/1/01 that the cases were being filed in the name of BMS Company. For the sake of clarification, if a provisional was filed prior to 10/1/01 and we are now doing the non-PCT countries filing and/or the PCT filing, whose name are we filing in?

Lori"

41. Ms Leung has suggested that the email of 24th October 2001 was consistent with an already extant general policy. Yet by January 2002, Mr Ferguson, replying to Ms Allaire (who is clearly unaware of any policy) felt the need to compel a significant number of people on his reply to Ms Allaire's query. (And there was a succeeding email of 1st February 2002, sent by Ms Allaire to some dozens of people advising them of Mr Ferguson's response.)

42. Why were these emails sent? Over two decades later, I do not really know. But neither do I see that I need to know, because (again) the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point.

43. There are also a couple of emails from March 2002 to which I was referred by counsel for Teva. These appear in the following order in the printout that is in evidence (with the earliest email, as usual, being at the bottom):

"*To: Carini, David…*
From: Blair Q Ferguson…
Sent: Tue: 3/26/2002 2:51:38 PM (UTC)
Subject: Re: [Fwd: [Fwd: Proper Use of BMS Pharma]

All cases having a provisional filing date on or after 10/1/01 will be assigned to BMS. All cases having a provisional filing date before 10/1/01 should be assigned to BMS Pharma.

Thanks for checking.

David J Carini wrote;

Blair, I had to leave assignment papers for a CDK patent redone in the name of BMS Pharma after they

were initially done in the name of BMS. I assume that this was done because the initial invention and/or filing was done in DPC. Is it the invention or the provisional filing that must have occurred when we were still DPC to make it a BMS Pharma case?

Subject: [Fwd: Proper use of BMS Pharma]
Re-sent from: MG-PRI-DISCOVERY-WILMINGTON…
Date: Tue, 26 Mar 2002 07:44:28-0500
From: Theresa R Stewart…
Organization: BMS
To:MG-PRI-DRUG-DISCOVERY-WILMINGTON…MG-PRI-NON-PRI-WILM…MG-PRI-CW-ALL

Please read the following important message…

Subject: Proper use of BMS Pharma…
Date: Mon. 25 Mar 2002 17:24:19-0500
From: David J. Roper
Organization: BMS
To: Theresa R Stewart
Cc: Paul Anderson…Blair Q Ferguson

Theresa

The Legal Department would like the following message [to be] sent to all BMS employees at the Experimental Station and Chambers Works to clear up the confusion about the use of the name BMS Pharma. If you would arrange to have the message sent to these employees it would be greatly appreciated.

Best regards

David

To all employees at the Experimental Station and Chambers Works:

This email is being sent to clear up the confusion that exists concerning the use of the name BMS Pharma. [There appears to be a few words missing from the segment of text placed before me but what is clearly meant to follow is that BMS] acquired DuPont Pharmaceuticals Company (DPC) on October 1, 2001. BMS changed the name of DPC to…BMS Pharma….The name change for DPC has resulted in confusion about whether the DPC employees in the Wilmington area who were retained by BMS are employees of BMS Pharma or of BMS and whether the retained DPC employees in the Wilmington area should be using BMS Pharma on scientific publications, stationery, and business cards.

All employees of DPC in the Wilmington area who were retained by BMS at the Experimental Station or Chambers Works are now employees of BMS, not BMS Pharma. As a result, the name of BMS Pharma should not be used in day-to-day activities. The guidelines for the use of BMS Pharma are as follows:

1. The business name given to third parties should be BMS, not BMS Pharma.
2. Business cards and business stationery should have BMS on them, not BMS Pharma.
3. Scientific presentations and papers should only refer to BMS, and authors and presenters should refer to themselves as employees of BMS, not BMS Pharma.
4. Inventions originating from scientists in the Wilmington area after October 1, 2001 should be assigned to BMS, not BMS Pharma.
5. Agreements should be executed in the name of BMS instead of BMS Pharma unless there is a legal reason to have BMS Pharma execute the agreement. One of the few circumstances in which an agreement would be executed in the name of BMS Pharma would be when the agreement is an extension of or an amendment to a former DPC agreement that is still in force.

In summary, the name BMS Pharma should not be used by BMS employees (except in the rare instance mentioned above). If there is a question about whether BMS Pharma should be used in a particular situation, the question should be directed to the Legal Department located…at the Experimental Station."

44. Why were these further emails sent? Again, over two decades later, I do not really know. But neither do I see that I need to know or to reach a conclusion in this regard, because (again) the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point.

10. The BMS Emails of 2002 – Part 2: The Administrative Training Manual

45. Later in 2002, on 12th June, an email with the subject heading "*Administrative Training Manual*" was sent by Ms Dora Lynch to a wide array of individuals that included Mr Ferguson, Ms Maureen O'Brien (a senior counsel), Mr David Bonk (head of the Patent Department, it seems), and Ms Barbara Bucchino, another lawyer. This email reads as follows:

> "*Enclosed is the updated training manual. We will be discussing this in our meeting tomorrow. You can keep all the sample documents that you have and simply replace the chapters. There are changes in almost every chapter regarding fees etc. but the chapters that have significant changes since you first got your original of this Manual are…Chapter 13: Assignments*"

46. The email continues:

> "*The procedures in this manual are updated as changes in PTO Rules change, or a Department Procedure changes. Anastasia Winslow has been assigned to me regarding rule changes at the PTO and updates me when something needs to be changed in the Manual to reflect the new rule. This manual will be constantly updated to reflect any changes necessitated by PTO rule changes or internal department changes and should be adhered to by all three sites.*
>
> *I understand that some of us who have been doing the job for years do not need to read the Manual in order to get something out to the PTO. However, there are department procedures in this manual that should be followed by all three sites. If you are not replacing the existing chapters with the updated chapters that I send from time to time, you may be continuing to follow procedures that are no longer in place.*
>
> *This manual was written for a definitive reason, to get uniformity and consistency and not be re-inventing the wheel. It is not that the procedures that I am giving you are 'right' and anything else is 'wrong'. However, this will be the base from where we start, and I'm sure we'll have many discussions among the attorneys to evolve this training manual into something that is acceptable to all. The point is that the collective attorney group can agree to make changes, but no individual attorney can make procedural changes...*
>
> *Dora*"

47. As will be seen, in Teva's examination of Mr Brown and its cross-examination of the other in-house BMS witnesses we spent an awfully long time on the issue of whether the emails of October 2001 and/or this manual constituted a policy or not and the legal import of this policy (if policy it was). While this focus was understandable in the course of the proceedings (because Teva obviously did not know what I would decide – and neither did I until the hearings ended and I deliberated on matters) I have concluded that the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point.

48. Page 84 of the manual attracted no little interest at the proceedings. Echoing in part Mr Ferguson's email of 30th January 2002, it states:

> "*All DuPont Pharmaceutical Company (DPC) cases which claim priority to a filing date prior to 10/1/01 should be in the name of...BMS Pharma….Thus, if the provisional is filed prior to 10/1/01, all subsequent filings worldwide should be in the name of BMS Pharma. BMS Pharma is a Delaware general partnership. For all*

Wilmington cases having an earliest priority date after 10/1/01, the name of [the] *assignee should be…BMS.*

You will prepare a new assignment for execution by the inventors when the case is filed as non-provisional. If you are getting the declaration signed prior to filing also get the assignment signed and submit for recordation with the filing papers. You will follow the same procedure for preparing the assignment as you did for the provisional application. If you are not submitting the assignment with the filing papers, wait until you receive the filing receipt before faxing for recordation."

49. As can be seen, the manual is a relatively formal document and the admonition that "*the collective attorney group can agree to make changes, but no individual attorney can make procedural changes*" suggests that the attorney group had imputed into the manual or, at the least, discussed it and given it some form of imprimatur. It seems to me that the existence and substance of the manual is consistent with BMS's contentions as to the level of control that BMS Co has always enjoyed over BMS Pharma. 'This aspect of these proceedings falls to be decided as a matter of Delaware law, and the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point.

11. Some Aspects of the Replies to Particulars

50. Moving on, counsel for Teva also brought me to some aspects of the replies to particulars, most notably Particular 5. It is worth quoting that particular in some detail as it touches on some central aspects of these proceedings and the substance of the dispute between the parties:

"*5. Original Request.*	*Please provide full particulars of the respondent's general plea that the respondent can validly claim priority from US165 for the patent. Please state the factual and legal basis for that plea.*
Reply.	*This request is misconceived, it is the petitioner which has pleaded in its amended particulars of objection that the patent cannot claim priority from US165 on a specific basis, namely that priority was claimed by a person who did not have the original right and who was not a successor in title of that person. The respondent has denied the allegation in that pleading while admitting the existence of documents referred to by the petitioner in its challenge. The full discovery requested by the petitioner in respect of the priority issue has been agreed to be given. The issue is defined and its resolution is a matter for legal argument, which will of course be outlined in legal submissions in due course.*
Further request.	*This is an inadequate response. The petitioner is entitled to know the basis upon which the respondent maintains, and positively pleads, that it can validly claim priority from US165 for the patent. Neither the factual nor legal basis for the respondent's claim is identified in the amended points of defence. The foregoing reply is tantamount to an outright refusal to provide basic particulars of that plea. It is an insufficient answer to state that the respondent's argument will be outlined in legal submissions in due course. The request per the original request 5 is repeated herein.*
Further reply.	*The US provisional application US165 from which EP415 claims priority was filed on 21st September 2001*

in the names of the inventors Dr Donald J Pinto and Dr Mimi L Quan. At that time Drs Pinto and Quan were employed with DuPont Pharmaceuticals Company. On 1 October 2001 the DuPont prescription drug business was acquired by BMS Company. That purchase entailed the transfer of the shares in DuPont Pharmaceuticals Company to ER Squibb and Sons, LLC and BMS Pharma Holding Company. DuPont Pharmaceuticals Company changed its name to BMS Pharma upon the transfer. Of its holding companies, BMS Pharma Holding Company was a wholly owned subsidiary of ER Squibb and Sons LLC and that company was itself a wholly owned subsidiary of BMS Company. Accordingly, as of 1 October 2001, BMS Pharma was the wholly owned subsidiary of BMS Company. Under the law of the State of Delaware, the residence of all of the relevant BMS companies in this matter, including BMS Pharma (formerly DuPont Pharmaceuticals Company) and the applicable law regarding the powers and functions of those companies and the ownership of the assets between them, a parent company can direct that a wholly owned subsidiary manage its property and affairs in the manner that the parent company requires. In this case BMS Company assumed control over the intellectual property of BMS Pharma including by determining the manner in which it was to be held. Under Delaware law, this power to control and direct the use and disposal of the said intellectual property constituted BMS Company as its beneficial owner. On 3 November 2001, Drs Pinto and Quan assigned to BMS Pharma all rights in US165 and the invention disclosed in it, together with all rights of priority or other rights attaching to it. On 17 September 2002, international application WO652 claiming priority from US165 and seeking registration as a European patent among others (and which resulted in EP1 427 415 and ultimately the patent in suit) was filed in the name of its inventors (for the US part) and BMS Company (for ex-US parts). WO652 was accordingly applied for by the owner of the beneficial interest in the right to priority, namely BMS Company. On 23 April 2007, BMS Pharma entered onto a form of assignment with BMS Company effective to transfer the legal interest in US165, any application claiming priority to it and related patents, including the legal interest in the right to claim priority to US165, to BMS Company. On 13 December 2016, BMS Pharma entered into a confirmatory form of assignment with BMS Company in respect of, inter alia, US 165. On 10 December 2015, BMS Company assigned the patent in suit to the respondent."

51. Further particulars are provided by the solicitors for BMS in a letter of 7th February 2022, which states, amongst other matters, as follows:

"[Question] *5.1 Please clarify whether it is the respondent's case that BMS Company was the beneficial owner of US165 by reason of the existence of a power to control its*

subsidiary's property.

[Reply] *Without prejudice to the legal argument to be made at trial, as a result of its 100% ownership of BMS Pharma and as a matter of the law of Delaware, BMS Company had the right to direct that BMS Pharma manage its property and affairs in the manner that BMS Company requires; this right was actively engaged by BMS Company in respect of the intellectual property of BMS Pharma by laying out the policy governing the manner in which the intellectual property of BMS Pharma was to be held. Under the law of Delaware these matters constituted BMS Company as beneficial owner of US165*".

52. In the same letter, there is also reference to Question 5.2 and a reply given:

"[Question] *5.2 If it is so asserted* [i.e. as stated in Question 5.1]*, please particularise the factual and legal basis of that claim.*

As already particularised the right of control of BMS Company over intellectual property of BMS Pharma arose under Delaware law as a result of its acquisition of 100% ownership of that entity. As indicated, upon acquisition, BMS Company exerted its right of control by laying out the policy as to how patents were to be held as between the companies such that ownership of existing patent and trademark rights related to the pharmaceutical business of BMS Pharma should remain in that company."

53. I note these exchanges. I deal with the substantive dispute between the parties later below.

12. The Supposed Evolution of BMS's Priority Case

54. After taking me through the substance of this dispute, counsel for Teva provided me with a helpful summary of the BMS position on legal/beneficial ownership, prior to the commencement of the hearings. This summary was provided in a bid to show me how changed BMS's case has been during the run-up to the proceedings. In its written closing submissions, Teva refers in this regard to "*countless reformulations, none of which was borne out by the evidence, or implemented consistently*". In fact, it seems to me that there has been a consistent adherence by BMS to the Control Proposition. That Control Proposition falls to be adjudged upon by reference to Delaware law and in this regard (i) I am confronted with the Common Delaware Evidence, and so (ii) the Paragraph 10 Point again falls to be made.

55. Teva's summary was provided to me in tabular form. I have abandoned that form and replicated the detail in a form more suitable for this judgment:

1. Dates: 23rd April 2007; 13th December 2016.
Location: 2007 and 2016 Assignments.

BMS Stance. (i) BMS Pharma assigned to BMS Company the "*entire right, title and interest in US 165*", expressly including the right to claim priority therefrom. (ii) 2007 Assignment: "*the right to claim priority for the above patent applications under the International Convention for the Protection of Industrial Property and under any other international arrangement to which the USA is or hereafter becomes a signatory*". (iii) The 2016 Assignment included "*the right to claim priority under the Paris Convention.*"

[As became clear during the oral testimony (considered later below) these years-later assignments use expansive wording as part of a standard 'belt and braces' approach to ensure that nothing was left behind. It goes

without saying that such assignments did not and could not negate or nullify any previous accrual of rights in favour of the other party to the instrument or a third party who is not privy to the instrument (and in this regard I note the Common Delaware Evidence).

In passing, I note that Teva suggests in its written closing submissions that BMS could have taken an alternative approach to protecting its interests in the impugned patent. Thus, it states:

> "*First, the Inventors could have assigned their interests to BMS Co. rather than BMS Pharma"*
>
> and
>
> *"Second, and alternatively, BMS Pharma could have assigned its interest in US165 onwards to BMS Co. at any time before the Filing Date*".

Three points might be made in this regard. First, it is true that BMS might have taken an alternative approach; however, the fact is that it did not and this case falls to be decided by reference to what BMS did, not by reference to what it might have done. Second, just because BMS might have taken an alternative route to the one it adopted does not point necessarily to there being any legal deficiency, from a Delaware law perspective, in the Control Proposition. Third, one might contend that the fact that BMS took the route it did and did not choose some other route speaks to its satisfaction, from a legal and practical perspective, as to the correctness of the Control Proposition as a matter of Delaware law (and the Common Delaware Evidence is supportive of that Control Proposition).]

2. Date: 25th October 2021
Location: Statement of Ms Marla Mathias (§§2 and 3)

BMS Stance: BMS (Ms Marla Mathias and Ms Dora Lynch) reviewed the patent docketing arrangements and renewal systems so that BMS "*could integrate the management of patents held by DuPont into BMS's own system*", and Ms Mathias supervised the "*integration of patent docketing and renewal arrangements of what was then BMS Pharma into those of BMS*".

[This is consistent with BMS's contentions as to the level of control that BMS Co has always enjoyed over BMS Pharma. 'This aspect of these proceedings falls to be decided as a matter of Delaware law, and the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point.]

3. Date 25th October 2021
Location: Statement of Ms Mathias (§3)

BMS Stance: (i) "*We did not take any steps to transfer legal title to the patents and patent applications held by what was then BMS Pharma Co to BMS*". (ii) "*It was a 'no brainer' to leave them where they were as we*

had access to them anyway". (iii) "[T]*here was no need to transfer legal title, and it would have made no sense to do so, as BMS was able in effect to treat BMS Pharma Co as a bucket out of which the intellectual property rights which it held at the closing could be withdrawn as necessary or otherwise deployed*." (iv) The way BMS Pharma was "*holding such intellectual property*" is set out in the email of 19th October 2001 which states "*BMS Pharma houses most of the intangibles, the acquired sites and realty…and pharmaceutical operations formerly operated by DuPont*". (v) Further relies on the email of 24th October 2001 and comments "*this email was memorializing decisions and planning that had been underway since June*." (vi) "*Leaving everything related to the pharmaceutical business in BMS Pharma Co…had surely been the default one from nearly the beginning of our due diligence*." (vii) "*As for the statement 'new patents and trademarks in the name of BMS Co' this would have reflected the integration of the ongoing activities of DuPont Pharmaceuticals into those of BMS, so one would expect subsequent patent filings to be made in the name of BMS*".

[See comments re.2.]

4. Date: 25th January 2022.
Location: Replies to Particulars, §5.

BMS Stance: "*In this case BMS Company assumed control over the intellectual property of BMS Pharma including by determining the manner in which it was to be held. Under Delaware law this power to control and direct the use and disposal of the said intellectual property constituted BMS Company as its beneficial owner.*"

[See comments re.2.]

5. Date: 7th February 2022
Location Replies to Particulars, §5.1

BMS Stance: "*As a result of its 100% ownership of BMS Pharma and as a matter of the law of Delaware, BMS Company had the right to direct that BMS Pharma manage its property and affairs in the manner that BMS Company requires; this right was actively engaged by BMS Company in respect of the intellectual property of BMS Pharma by laying out the policy governing the manner in which the intellectual property of BMS Pharma was to be held. Under the law of Delaware these matters constituted BMS Company as beneficial owner of US165*."

[See comments re.2.]

6. Date: 7th February 2022
Location: Replies to Particulars, §5.2

BMS Stance: "*BMS Company exerted its right of control by laying out the policy as to how patents were to be held as between the companies such that ownership of existing patent and trademark rights related to the pharmaceutical business of BMS Pharma should remain in that company*".

[See comments re.2.]

7.Date: 21st March 2022.
Location: Witness Statement Paul Golian (§4 and §8, and email 19 October 2001 at PG1)

BMS Stance: BMS Pharma is a wholly owned subsidiary of BMS Co., a Delaware partnership, currently owned 50% by ER Squibb & Sons LLC and 50% by BMS Pharma Holding Company LLC (which is 100% owned by ERS).

[See comments re.2.]

8. Date: 21st March 2022
Location: Witness Statement Paul Golian (§6 and 7) and emails exhibited at PG1 and PG2

BMS Stance: "*BMS Co made the decisions as to how it and its wholly owned subsidiaries hold their intellectual property assets, including prior to its acquisition of the DU Pont pharmaceuticals business", which "is borne out by the emails dated 19th October 2001 and 29th October 2001*".

[See comments re.2.]

9. Date: 21st March 2022.
Location: Witness Statement Paul Golian (§11 and the email of 24th October 2001 exhibited at PG2)

BMS Stance (i) "*Email* [of 24th October 2001] *reflects the decision making by BMS Co as to the legal ownership of BMS Pharma Co's intellectual property and the putting in place of a policy in that regard. (ii) BMS Co [is] the decision maker and having control over how the intellectual property assets of its wholly owned subsidiaries are to be held.*"

[See comments re.2.]

10. Date: 21st March 2022
Location: Witness Statement: Paul Golian (§12) and email of 24th October 2001

BMS Stance: (i) "*The policy described in [the 24th October 2001] email, whereby legal ownership of BMS Pharma, pharma IP assets remained with that entity and only required a name change from DuPont Pharmaceuticals Company to BMS Pharma*". (ii) 24th October 2001 email refers to: recommendations by lawyers to "*maintain legal ownership in BMS Pharma (formerly DPC)*" in respect of existing rights always residing there. "*New patents and trademarks in the name of BMS Company.*" (iii) "*Effecting name changes less costly/time consuming than it would have been to have BMS Pharma assign all those rights to BMS Co.*" (iv) "*As appears from the October 2001 emails, BMS Co had control over the ownership of those intellectual property assets such that it could have decided to have BMS Pharma assign those intellectual property assets to it at a later date as and when required*."

[See comments re.2.]

11. Date: 21st March 2022.
Location: Email of 24th October 2002 (exhibited at PG2)

BMS Stance: "*(1) Patents and trademarks related to the pharmaceutical business – maintain legal owners in BMS Pharma (formerly DPC). We believe that this is the entity where they currently reside, so this should involve only a name change. New patents and trademarks in the name of BMS Company.*"

[See comments re.2.]

12: Date: 21st March 2022.
Location: Witness Statement Paul Golian (§13)

BMS Stance: On 17th September 2002 BMS Co filed international patent application PCT491 (which became Patent EP (IE) 415 claiming priority from US165 at which time "*BMS Pharma was a wholly owned subsidiary of BMS Co and subject to its control and direction*".

[See comments re.2.]

13. Date: 2nd August 2022
Location: Witness Statement Sandra Leung (§12)

BMS Stance: (i) BMS is organised with a centralised corporate structure – BMS Co is the ultimate parent company of the BMS Group. "*As a result of this centralised structure, all IP – regardless of which of BMS Co's wholly-owned subsidiaries held legal title – is and was held for the ultimate benefit of BMS Co.*" (ii) BMS Co had and has "*control over how the IP assets and associated IP rights of its wholly owned subsidiaries are held*". (iii) BMS had and has a single IP department for all of BMS. This department "*managed the IP assets of BMS for the ultimate benefit of BMS Co*". (iv) "*In particular, this IP department in the relevant time, and since then exercised ultimate control over the location and disposition of all IP, including for any IP rights to claim priority, held by any BMS companies*."

[See comments re.2. Some attempt was made at the hearing and again in Teva's written closing submissions to suggest that Ms Leung was not right in her averments to suggest that what she stated applied also to BMS Holdings Ireland Unlimited Company. However, at the earliest opportunity Ms Leung corrected what she meant to state in this regard and, in truth, this was something of a 'side show' given the Common Delaware Evidence (which in turn leads inexorably to the Paragraph 10 Point).]

14. Date: 2nd August 2022.
Location: Witness Statement Sandra Leung (§13)

BMS Stance: (i) "*It was common practice at the relevant time and through today that when BMS acquires another company, legal title to the other company's IP is left in place with the acquired subsidiary, which is wholly owned, directly or indirectly, but* [by?] *BMS Co, rather*

than having such legal title assigned to BMS Co.". (ii) "[B]*ecause the subsidiary was wholly owned by BMS Co it was not and is not relevant to BMS whether or not the legal title to the IP was actually held by BMS Co. This is because BMS as the ultimate parent company has and had during the relevant time, the ability to exercise ultimate control over any IP rights regardless of which of its wholly owned subsidiaries may hold legal title to the IP.*"

[This is consistent with BMS's contentions as to the level of control that BMS Co has always enjoyed over BMS Pharma. This aspect of these proceedings falls to be decided as a matter of Delaware law, and the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point. During Teva's opening submissions, counsel for Teva pointed to Ms Leung's witness statement as being the first statement in which reference was made to the control proposition. That may be so; however, as I have made clear in the foregoing text this proposition was expressly identified by BMS on multiple occasions from January 2022 onwards. The Control Proposition falls to be adjudged upon by reference to Delaware law and in this regard (i) I am confronted with the Common Delaware Evidence, and so (ii) the Paragraph 10 Point again falls to be made.]

15. Date: 2nd August 2022.
Location: Witness Statement Sandra Leung (§14)

BMS Stance: (i) "[F]*ollowing the acquisition of DuPont Pharma by BMS Co., BMS Co made the decision to leave the IP assets held by DuPont Pharma with that entity which was wholly owned by BMS Co and BMS Co merely changed the name of that entity to BMS Pharma*". (ii) "*BMS Co., nonetheless as the ultimate parent company, exercised control over and was the beneficial or equitable owner of all IP rights held by BMS Pharma*".

[See comments re.2.]

16. Date: 2nd August 2022.
Location: Witness Statement Sandra Leung (§16)

BMS Stance: (i) "*Since a primary purpose of BMS Co's acquisition of DuPont Pharma was to strengthen its virology and cardiovascular franchises through the acquisition of the 'Du Pont Pharma Assets', BMS Co would necessarily need to be in control of the IP rights, in particular patent rights that protect those DuPont Pharma assets*". (ii) "[I]*t would only have made sense to, and BMS Co would only have agreed to, house the patents protecting the DuPont Pharma Assets in BMS Pharma if BMS Co had the beneficial/equitable ownership of, and the ability to control those patents.*" (iii) "[D]*uring the relevant time, BMS Pharma was a wholly owned subsidiary of BMS Co and was subject to its control and direction. Further, BMS Co was the beneficial and equitable owner of any IP rights held by BMS Pharma.*"

[See comments re.2.]

17. Date: 2nd August 2022.
Location: Witness Statement Sandra Leung (§17)

BMS Stance: (i) "*How we handled the DuPont Pharma acquisition is consistent with BMS's longstanding general policy and practice that continues today of leaving all the acquired IP in a wholly owned subsidiary for the benefit of BMS Co.*" (ii) "[W]*hen BMS Co acquires an asset, we generally keep the assets of that entity in that entity, but it is held for the ultimate benefit of BMS Co and BMS Co wholly owns that entity and has the right and ability to control that IP*". (iii) "*This policy makes sense given the way BMS is and was at the relevant time structured and operated*."

[See comments re.2.]

18. Date: 2nd August 2022.
Location: Witness Statement Sandra Leung (§19)

BMS Stance: The October 24th 2001 email sets out recommendations…for the legal entity registration of various IP assets of the DuPont pharmaceuticals business.

[See comments re.2.]

19. Date: 2nd August 2022.
Location: Witness Statement Sandra Leung (§20)

BMS Stance: (i) "*This recommendation in this email is in accordance with the decision making and general policy and practices of BMS Co described above whereby acquired IP is often left in the acquired wholly owned subsidiary*." (ii) "*Specifically, legal ownership of BMS Pharma's IP assets remained with DuPont Pharmaceuticals Company and the name…was later changed to the new name, BMS Pharma*". (iii) "*Again, BMS Co was the ultimate parent company of BMS Pharma and was the beneficial owner of such IP assets and controlled how IP rights of its wholly owned subsidiaries were held*". (iv) "*There was no need for BMS Co to place the IP assets acquired from DuPont in BMS Co at any particular time because it maintained control over the IP at all times and could decide to have BMS Pharma assign those IP assets to it (or any other entity) whenever it wished to do so when it served a business purpose, as it did so here*".

[See comments re.2.]

20. Date: 2nd September 2022.
Location: Replying Affidavit of Shane O'Brien (first Interrogatories Motion) (at §39)

BMS Stance: It is BMS's case that "*BMS Co already held the beneficial interest in the priority document such that it was not among the rights retained by BMS Pharma to give.*"

[See comments re.2.]

21. Date: 2nd September 2022.
Location: Replying Affidavit of Shane O'Brien (first interrogatories motion) (at §41).

BMS Stance: "[T]*he Respondent emphasised the central point in this case, namely that BMS Company controlled BMS Pharma's intellectual property and that the 24th October 2001 email was evidence of the proposed policy at that point*."

[See comments re.2.]

22. Date: 13th October 2022.
Location: Transcript of First Interrogatories Motion on 13th October 2022 at 33-34

BMS Stance: BMS confirmed that the policy evidenced by 24th October email was in fact implemented. [It is not necessary to recite the extract from the submissions made to O'Moore J. in this regard].

[If one raises an interrogatory, one typically gets an answer. Here, BMS had an interrogatory put to it and provided an answer. That does nothing to change its consistent adherence to the Control Proposition. The Control Proposition falls to be adjudged upon by reference to Delaware law and in this regard (i) I am confronted with the Common Delaware Evidence, and so (ii) the Paragraph 10 Point again falls to be made.]

23. Date: 10th March 2023.
Location: Reply to Interrogatory §5.17

BMS Stance: Reply to Interrogatory 5.17, BMS rely on the email of 24th October 2001 as evincing the policy upon which it relies. The email refers to recommendations by lawyers to "*maintain legal ownership in BMS Pharma (formerly DPC)" in respect of existing rights already residing there. "New patents and trademarks in the name of BMS Company.*"

Interrogatory 5.17 stated:

"*5.17 Did not BMS Company lay out the policy as to how patents were to be held as between BMS Company and BMS Pharma?*

Answer: More precisely, it laid out the policy as to 'legal entity registration' of patents from the acquired DuPont pharmaceutical business which was to 'maintain legal ownership in BMS Pharma' in respect of existing rights already residing there and to put new patents and trade marks in the name of BMS Company.

Response: Insufficient reply. If 'it' is intended as a reference to the email of 24th October 2001, does not that email concern a 'recommendation' by the tax department of BMS Company and not a decided policy of any entity? Is it not erroneous to state that the email of 24th October 2001 contains a single policy or recommendation "…as to 'legal entity registration' of patents from the acquired DuPont pharmaceutical business'? Rather, is it not the case that there was a recommendation for

different treatment of different categories of 'Du Pont Pharma' patents and trademarks?

Further Answer: BMS Co controlled how the intellectual property acquired in the DuPont acquisition should be held and dealt with. The email of 24th October 2001 is evidence of part of that process whereby the proposed policy at that point, just after acquisition, as to how the rights were to be held was circulated and comment invited. The implementation of the policy is the province of oral evidence to be given at trial."

[See comments re.2.]

24. Date: 10th March 2023.
Location: Reply to Interrogatory 5.19

BMS Stance:

"*5.10. Was not the policy of BMS Company set out in the email of 19th October 2001 and 24th October 2001.*
Answer: The policy concerning "legal entity registration" and "legal ownership" of patents arising from the acquired business was set out in the email of 24th October.
Further Answer: Please see the supplemental response to 5.17."

[See comments re.2.]

25. Date: 10th March 2023
Location: Interrogatories Affidavit of Scott Brown (at §9)

BMS Stance: Reply to Interrogatory 5.20

"*To the best of my knowledge, information and believe* [sic- belief]*, other than the emails of 19th October 2001 and 24th October 2001, the 'said policy', that is the decision to maintain legal ownership in BMS Pharma in respect of existing rights already residing there and to put new patents and trade marks in the name of BMS Company was evidenced in writing in the following materials which I outline in the paragraphs below.*"

[See comments re.2.]

26. Date: 10th March 2023.
Location: Administrative Training Manual issued 6th June 2002, "SB2"
p.84 of 116

BMS Stance: Chapter 13 of the Manual reads as follows:

"*All Du Pont Pharmaceutical Company (DPC) cases which claim priority to a filing date prior to 10/1/01 should be in the name of…BMS Pharma….Thus, if the provisional is filed prior to 10/1/01, all subsequent filings worldwide claiming this priority should be in the name of BMS Pharma. BMS Pharma is a Delaware general partnership. For all Wilmington cases having an earliest priority date after 10/1/01, the name of assignee should be BMS….You will need to change the Recordation Cover Sheet to enter BMS Pharma…as the form defaults to BMS*

Company".

[See comments re.2.]

27. Date: 10th March 2023.
Location: Email 30th January 2002 (at "SB2", p.10 of 116)

BMS Stance: "Any patents filed before 1 October 2001 should be filed in the name of BMS Pharma and – very significantly – that "*all subsequent filings worldwide claiming this priority should be in the name of BMS Pharma*", *i.e.* not BMS Co.

[See comments re.2.]

28. 6th April 2023.
Location: Letter from McCann Fitzgerald (for BMS) to Pinsent Masons (Ireland) (for Teva)

BMS Stance: "*Subject to what our client's witnesses may say, the documents appear on their face to represent clarification being sought and given in relation to how applications were to be determined as predating or post-dating the acquisition of the rights in question. We are having difficulty understanding how this is said to be at odds with our client's case of central control.*"

[See comments re.2.]

29. 24th April 2023.
Location: Court of Appeal Submissions
(Failed Appeal Against Injunction).

BMS Stance "*Our case is control. That control is evidenced by, for example, the policy…'*"
"[I]*f, for example, I had a different policy for every day of the week, I am exercising control because I am the parent telling the subsidiary how that asset is to be handled. Whether that be by way of giving me an assignment to it, whether that's by way of change of name, leaving the original filing in the name of that wholly owned subsidiary…It's the power of control…'.*[3]

[referring to the manual] "*It's not inconsistent with the emails. But it may be the case that the policy wasn't followed in respect of that particular application here. But that, of course, is entirely beside the point and irrelevant. Because what is happening is BMS Co exercising control*"

[See comments re.2.]

[3] Teva has contended in this regard that (i) the notion that the mere existence of a policy evinces proof of control is remarkable, and that (ii) if one was to follow this logic through to its natural conclusion the more one changed a policy the more one would evidence control. I do not see that point (i) has ever been contended for by BMS. As to point (ii), the control/priority aspect of these proceedings falls to be decided as a matter of Delaware law, and the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point.

30. Date: 26th May 2023.
Location: Letter from McCann Fitzgerald (for BMS) to Pinsent Masons (Ireland) (for Teva)

BMS Stance: "*The reasonable interpretation of [the October 2001 emails and the documents provided with the Interrogatories Affidavit] appears to us to be that they provide, in the context of patent filings, as to what was to be considered a 'new' patent, as the term is used in the October 2001 emails*."

[See comments re.2.]

31. Date: 26th May 2023.
Location: Letter from McCann FitzGerald (for BMS) to Pinsent Masons (Ireland) (for Teva)

BMS Stance: "*In particular Mr Golian will give evidence that the guidance in question reflects his memory of what was the general practice in the BMS patent department when he joined it is consistent with the decision that was made to leave all existing patents in BMS Pharma with new patents to be in the name of BMS Co can be seen as providing guidance as to what is to be considered a 'new' patent for that purpose, and is consistent with BMS Co being the decision maker in that regard and having control over the IP of BMS Pharma.*"

[See comments re.2.]

32. Date: 29th May 2023.
Location: Transcript, 29th May 2023, p.22

BMS Stance: "*The policy that is now there, we respectfully say, that it is simply saying which are old rights and which are new rights.*"

[This is consistent with BMS's contentions as to the level of control that BMS Co has always enjoyed over BMS Pharma. This aspect of these proceedings falls to be decided as a matter of Delaware law, and the Control Proposition is supported by the Common Delaware Evidence, leading inexorably to the Paragraph 10 Point].

33. Date: 20th June 2023.
Location: Written Submissions, §135.

BMS Stance: "[T]*he arrangements in question were made by BMS Co in exercise of its enforceable control of, and therefore its beneficial interest in, the intellectual property of BMS Pharma.*"

[See comments re.2.]

34. Date: 20th June 2023.
Location: Written Submissions, §136

BMS Stance: "*They* [the discovery documents] *are not internally contradictory and merely show the working out of the application of the policy. The key point however is that they all go to show that it was BMS Co that was prescribing what was to be done because it was in control of*

the intellectual property in question".

[See comments re.2.]

56. I do not see in the 34 steps described above an evolution of BMS's case from (as Teva would have one believe) (i) a position in which BMS company policy was identified in a trio of emails, to (ii) a legal/beneficial ownership proposition, initially identified by Ms Leung in August 2022, to (iii) a position where because a contradictory policy has been found to present, BMS adopts the fresh position that it does not matter what the policy is or states, it matters only that it exists. Rather, I see a consistent adherence by BMS, from January 2022 onwards, to the Control Proposition. The Control Proposition falls to be adjudged upon by reference to Delaware law and in this regard (i) I am confronted with the Common Delaware Evidence, and so (ii) the Paragraph 10 Point again falls to be made.

57. Given the above-suggested 'evolution' of BMS's position, a letter of 8th May 2023 issued from the solicitors for Teva to the solicitors for BMS querying what position BMS intended to adopt in the present hearing. That letter reads as follows:

"*Dear McCann FitzGerald*

As you know, there has been ongoing uncertainty and confusion as to the basis on which your client asserts its entitlement to rely on the priority date of 21st September 2001. This has been the subject of further and better particulars of pleading, interrogatories and debate during the motions that were heard by O'Moore J. in October 2022….While we have grave concerns about the persistent shifting of your client's case (and our position in that respect is fully reserved), our most pressing concern now, given the imminent commencement of the trial of the revocation proceedings is to try to understand the case your client in fact intends to make at that trial. The most recent articulation of this case was during the hearing before the Court of Appeal on 24th April 2023 in the Infringement Proceedings when the following submissions were made:

- *'our case is control. That control is evidenced by, for example, the policy'….*
- *'…if, for example, I had a different policy every day of the week, I am exercising control because I am the parent telling the subsidiary how that asset is to be handled. Whether that be by way of giving me an assignment to it, whether that's by way of a change of name, leaving the original filing in the name of that wholly owned subsidiary….It's the power of control)'….*
- [referring to the BMS manual] *'It's not inconsistent with the emails. But it may be the case the policy wasn't followed in respect of the particular application here. But that, of course, is entirely beside the point and irrelevant. Because what is happening is BMS Co exercising control'….*

From these submissions, it appears that the case now being made by your client is that, as a result of the 100% ownership of BMS Pharma, BMS Company had the right/power to direct how BMS Pharma managed its property and that this right/power constituted BMS Company as beneficial owner of the property of BMS Pharma, regardless of whether or how that asserted right/power was exercised and if exercised regardless of whether or how the policies set out by BMS Pharma in that regard were implemented. Can you please confirm that this is your client's case? If not please set out in clear and unambiguous rems what case your client considers it is entitled, and will seek, to advance at the trial."

58. This letter met with an entirely predictable response from the solicitors for BMS, stating as follows:

> "*You refer in your letter to an alleged 'shifting' of our client's case on priority, purport to characterise it in a tendentious, indeed eccentric, manner and then look either for 'confirmation' of that characterisation or another statement of our client's case. There has been no 'shifting' of our client's case. The attempt made on behalf of your client in the discovery and evidence motions of last October to assert such a 'shifting' failed. Our client has set out its case – in its pleadings and in replies to particulars. It is completely inappropriate to seek a parallel statement in correspondence. Not only has our client's case been pleaded and particularised, the manner in which our client will support its case in evidence has been set out in the witness statements filed on its behalf. The witnesses to be put forward by your client have engaged with those matters in their statements. Furthermore, our client has set out its legal argument on the basis of that pleading and intended evidence in written submissions. The idea that your client is at any loss in relation to identifying our client's case is fanciful, but your client may of course seek to take any point that it is minded to take in that regard at trial.*"

59. All I see in the foregoing is a surprising letter sent by Teva in May 2023 suggesting that Teva was confused as to the substance of BMS's case when the nature of same had been known (as I have shown above) since January 2022, and when the substance of BMS's case had been pleaded, particularised, and its legal arguments identified. In all those circumstances, I cannot but respectfully agree with the author of the letter of reply to Pinsent Masons (the solicitors for Teva) that the notion that, by May 2023, Teva, a litigant armed with the best of lawyers, could have been at any loss in identifying the case being advanced by BMS in the present proceedings as to priority was "*fanciful*". 'The Control Proposition falls to be adjudged upon by reference to Delaware law and in this regard (i) I am confronted with the Common Delaware Evidence, and so (ii) the Paragraph 10 Point again falls to be made.

13. Some Elements of the Assignments

60. Counsel for Teva turned next to the terms of the various assignments. So it is worth my pausing briefly to consider some elements of their detail.

61. The first assignment was the inventors' assignment of 3rd November 2001, in which Mr Pinto and Ms Quan effect an assignment to BMS Pharma, in which, amongst other matters, the assignors:

> "[s]*ell, assign and transfer unto BMS Pharma…(A) the sole and entire right, and interest in and to (1) the aforesaid application for letters patent, (2) any priority rights derived from the aforesaid application…*".

62. The next assignment is the assignment of 23rd April, 2007. This is an assignment from BMS Pharma to BMS Co of, amongst other matters:

> "*the entire right, title, and interest in all countries of the world in and to the patent application Ser No 60/324,165….This assignment includes the grant by the assignor to the assignee of the right to claim priority for the above patent applications under the International Convention for the Protection of Industrial Property and under any other international agreement to which the United States of America is or hereafter becomes a signatory.*"

63. The last assignment that falls to be mentioned is that of 13th December 2016 between BMS Pharma and BMS Company. In it BMS Pharma (as assignor), amongst other matters:

"*confirms that (i) it previously sold, assigned, transferred and delivered to the Assignee, and Assignee accepted all of the rights, title and interest in, to and under the Assigned Patents…*".

64. Two points might, perhaps usefully, be made by me regarding the assignments of 2007 and 2016:

(i) as mentioned above, Teva has sought to make great play of these assignments, suggesting that the rationale for same has never been explained by BMS (not that a duty of explanation arises). This is because, as a result of the Common Delaware Evidence, the most that can have been transferred in the assignments of 2007 and 2016 was BMS Pharma's legal interest. Thus, it seems to me to get one nowhere in the circumstances presenting to consider the wording of the assignments of 2007 and 2016 in any detail.

(ii) notwithstanding (i), in the course of the proceedings Teva focused on the fact that (a) in the 2007 assignment, BMS Pharma assigned to BMS Company the "*entire right, title and interest in* [US 165], expressly including the right to claim priority therefrom, (b) "*the right to claim priority for the above patent applications under the International Convention for the Protection of Industrial Property and under any other international arrangement to which the USA is or hereafter becomes a signatory*", (c) the 2016 assignment included "*the right to claim priority under the Paris Convention.*" Without prejudice to what I have stated at point (i) above, when it comes to Teva's focus on these aspects of the 2007 and 2016 assignments:

  (I) one can only assign what one has, and the thrust of the Common Delaware Evidence is that BMS Co would be found in Delaware to enjoy equitable ownership of BMS Pharma's intellectual property.

  (II) as became clear during the oral testimony (considered later below) these years-later assignments use expansive wording as part of a standard 'belt and braces' approach by whomever drafted the assignments to ensure that nothing was left behind.

  (III) it goes without saying that such assignments did not and could not negate or nullify any previous accrual of rights in favour of the other party to the instrument or a third party who is not privy to the instrument.

  (IV) as to Teva's contention that the assignments of 2007 and 2016 were somehow inconsistent with BMS's reliance on the Control Proposition, that inconsistency does not present when one has regard to the Common Delaware Evidence and the Paragraph 10 Point.

65. In its written submissions, Teva has helpfully summarised its case when it comes to the assignments in the below terms, which I quote at this point because it will help the reader to know precisely what case has been made by Teva in this regard:

"*4.14 In the present case, (a) there is no proof whatsoever of an assignment of US165, or of the right to claim priority therefrom, by the inventors or their successor in title, BMS Pharma to BMS Company prior to the Filing Date*

[i.e. 17th September 2002]; (b) BMS Company was not the holder or assignee of US165 on the Filing Date, and (c) US 165 was later assigned by BMS Pharma to BMS Company in 2007 and again in 2016. That being so, BMS Company cannot validly claim priority from US165 for the Patent.

4.15 *To seek to overcome this...difficulty, BMS makes the...argument that BMS Company was the owner of some sort of beneficial interest in the right to priority. BMS pleads that under Delaware law, a combination of two matters constituted BMS Company as beneficial owner of US 165 namely: (a) the power of BMS Company to direct that BMS Pharma manage its property and affairs in the manner that BMS Company requires; and (b) that this right was actively engaged by BMS Company in respect of the intellectual property of BMS Pharma by laying out the policy governing the manner in which the intellectual property of BMS Pharma was to be held.*

[As regards 4.14 and 4.15, I am confronted with the Common Delaware Evidence and would reiterate the Paragraph 10 Point in this regard.]

4.16 *This is factually and legally unfounded:*

a. *First, the unexplained assignments from BMS Pharma to BMS Company of the entire right, title and interest in US 165 in 2007 and again in 2016, flatly contradict the theory that BMS Company was already the beneficial owner of US 165.*

[This is answered by points I-IV immediately above.]

b. *Second, taken at its height the only basis tendered by BMS to substantiate the alleged 'putting in place of a policy in that regard' is a single statement in an email dated 24th October 2001: 'Maintain legal ownership in [BMS Pharma]…New Patents and Trademarks in the name of [BMS Company].'*

[Again, I am confronted with the Common Delaware Evidence and would reiterate the Paragraph 10 Point in this regard.]

b. *Third, BMS recently disclosed highly relevant documents which set out a clear policy, formulated by its chief patent counsel, and widely disseminated within BMS, over several years, as to the assignment and filing of patents between BMS Co and BMS Pharma. This policy flatly contradicts the recommendation in the 24th October 2001 email. The policy is recorded in an administrative manual and related emails which state, unambiguously, that all patent applications filed after 1st October 2001 but claiming a priority date prior to 1st October 2001…were to be filed in the name of BMS Pharma and not BMS Company….This did not occur in the present case.*

[Again, I am confronted with the Common Delaware Evidence and would reiterate the Paragraph 10 Point in this regard.]

c. *Fourth, a corporation and a limited partnership are separate legal entities under Delaware law, independent from its parent or subsidiaries. The parent-subsidiary relationship alone is insufficient to establish equitable title to a patent and does not equate to an assignment.*

[Again, I am confronted with the Common Delaware Evidence and would reiterate the Paragraph 10 Point in this regard.]

d. *Fifth, the height of BMS's pleaded case is that Delaware law provides that 'a parent company can direct…' how a subsidiary does certain things. To test the application of any such rule, clear evidence is required as to what the parent in fact did vis-à-vis its subsidiary. No such evidence has been presented.*

[Again, I am confronted with the Common Delaware Evidence and would reiterate the Paragraph 10 Point in this regard.]

e. *Sixth, BMS's theory of beneficial ownership overlooks the requirement of US federal law, which requires 'an instrument in writing' (35 USC §261) and BMS can point to none. That statute reflects a policy of legal and commercial certainty as regards the ownership of patents.*

[As will be seen from the evidence that follows, United States federal law does not operate to preclude my finding that BMS Co held the equitable interest contended for in US165.]

g. *Finally, the only EPO case identified by BMS's EPO expert [Mr Rennie-Smith] in which an equitable title was found to demonstrate succession in title under Art.87(1) EPC was J 19/87 (21st March 1988). In contrast with the present case where there is no assignment there was a formal assignment which was signed by the assignor but not the assignee. The Board held that the assignment did have certain legal effects. In particular, after this assignment was executed on behalf of the assignor, the assignee became the owner of the invention, became entitled in equity to the UK application and was entered on the register of patents in the UK. However, in later decisions, Boards have clarified with respect to J19/87:*

   i. *this is a 'particular situation' that should 'not be taken out of its context but should be confined to the facts of that case.' (T577/11 at 6.6.2)*
   ii. *'this conclusion [in J19/87] was drawn from a situation in which the relevant assignment agreement, by which ownership was to be transferred, was concluded prior to the filing of the subsequent application and was defective solely for formal reasons.' (T577/11 at 6.6.2)*
   iii. *'The formal defects in the assignment could have been remedied by the contracting parties at any moment after its conclusion, and this remedy was legally possible under English law' (T577/11 at 6.6.2)*
   iv. *The 'equitable assignment' was*

registrable on the UK patent register and registration had indeed taken place. (T577/11 at 6.6.2).

[This is not the point at which to consider European Patent Office case-law. I do so later below. As will be seen, I conclude that Art.87 of the European Patent Convention imposes (i) no requirement for an agreement or an assignment before a company can be regarded as successor in title to the priority right, and (ii) no constraint or block on equitable ownership of the priority document as a proper basis upon which to claim priority. (And no such requirements can therefore impact on the construction or implementation of s.25 of the Patents Act 1992, as amended.).]

4.17 *In light of the above, BMS has no factual basis to assert a right to priority from US165 and the relevant date for the assessment of the state of the art is the Filing Date* [17th September 2002] *and not the Claimed PD* [21st September 2001].

[In light of the Common Delaware Evidence, Teva, respectfully, is wrong in this contention.]"

14. Some United States and Delaware Law

66. Counsel for Teva turned next to some aspects of United States and Delaware law. I confine myself here to mentioning the statutory provisions that counsel mentioned. The expert evidence that I have read/heard on United States and Delaware law is considered later below.

67. In terms of federal law the legislation of interest is, of course, the US Patent Code, Title 35 USC, §261 (sitting in Chapter 26, "*Ownership and Assignment*"), so far as relevant to these proceedings, provides as follows:

"*§261. Ownership; assignment*

Subject to the provisions of this title, patents shall have the attributes of personal property. The Patent and Trademark Office shall maintain a register of interests in patents and applications for patents and shall record any document related thereto upon request, and may require a fee therefor.
Applications for patent, patents, or any interest therein, shall be assignable in law by an instrument in writing. The applicant, patentee, or his assigns or legal representatives may in like manner grant and convey an exclusive right under his application for patent, or patents to the whole or any specified part of the United States…".

68. Later, §261 continues:

"*An interest that constitutes an assignment, grant or conveyance shall be void as against any subsequent purchaser or mortgagee for a valuable consideration, without notice, unless it is recorded in the Patent and Trademark Office within three months from its date or prior to the date of such subsequent purchase or mortgage.*"

69. Issues of Delaware law also arise in these proceedings. Worth mentioning at this juncture is §220 of the Delaware Corporate Code. It provides, amongst other matters, as follows:

"*§220 Inspection of books and records…*

(2) "Subsidiary" means any entity directly or indirectly owned, in whole or in part, by the corporation of which the stockholder is a stockholder and over the affairs of which the corporation directly or indirectly exercises control, and includes without limitation, corporations, partnerships, limited partnerships, limited liability partnerships, limited liability companies, statutory trusts and/or joint ventures….

[(3)] *(b) Any stockholder, in person or by attorney or other agent, shall, upon written demand under oath stating the purpose thereof, have the right during the usual hours for business to inspect for any proper purpose, and to make copies and extracts from:*

(1) The corporation's stock ledger, a list of its stockholders, and its other books and records; and

(2) A subsidiary's books and records, to the extent that:

a. The corporation has actual possession and control of such records of such subsidiary; or

b. The corporation could obtain such records through the exercise of control over such subsidiary, provided that as of the date of the making of the demand:

1. The stockholder inspection of such books and records of the subsidiary would not constitute a breach of an agreement between the corporation or the subsidiary and a person or persons not affiliated with the corporation; and

2. The subsidiary would not have the right under the law applicable to it to deny the corporation access to such books and records upon demand by the corporation…".

70. As counsel for Teva observed in his opening remarks, the provisions of §220(3)(b) are clearly supportive of the notion that the concept of corporate separateness is a principle of Delaware law. As will be seen, this was not disputed by either of Messrs Chandler or Steele, the expert witnesses called to give evidence on Delaware law.

71. Moving on to §271 of the Delaware Code (in Subchapter X, "*Sale of Assets, Dissolution and Winding Up*"), it provides, among other matters, as follows:

"*§271 Sale, lease or exchange of assets; consideration; procedure*
(a) Every corporation may at any meeting of its board of directors or governing body sell, lease or exchange all or substantially all of its property and assets, including its goodwill and its corporate franchises, upon such terms and conditions and for such consideration, which may consist in whole or in part of money or other property….
(c) For purposes of this section only, the property and assets of the corporation include

the property and assets of any subsidiary of the corporation…".

72. The word "*only*" was inserted into subsection (c) following on a decision of Strine VC in *Hollinger, Inc. v. Hollinger International, Inc., 858 A.2d 342, 347 (Del. Ch. 2004)*, a case to which I turn later below.

15. Closing Remarks in Opening Comments on Priority

73. The closing remarks of counsel for Teva's opening remarks on the issue of priority might usefully be quoted at some length in giving a sense of the case that Teva has sought to make in this regard in these proceedings:

> "*So, that's the case in priority. From our perspective, with great respect, it is a clear case. They have lost priority. They have sought to create a construct that somehow now allows them* [to] *claim…beneficial ownership at one time…*[and] *control at another time. Both happily converge to give them…ownership. In what measure or what mixture or what formula, we don't know, but these two streams provide it. And as I say, it will all be revealed when they give their evidence as to how they equate this and how they explain this…policy by BMS Company that manages, as a multinational, to record…policy in a four-line e-mail that records* [as] *a fact that BMS Pharma was the legal owner and the legal ownership would be maintained. That statement of policy is developed by the witnesses in this case as meaning something very different from what it says. And as I say, it is a foundation of sand….*[and] *the sand has already shifted, it never provided a foundation, it is based on no legal principle that is recognisable, it is wrong in law and it is wrong in fact and they have not even, for the court, told the court how they square that policy with the evidence now before the Court…*[T]*he minimum that is to be expected of a multinational corporation, or of any litigant, no matter how modest, in a court,* [is] *that they would say 'This is our case and, yes, this document has come to light and here is the reason why I, with all my involvement in the patents and the legal side, missed this previously and this now is the explanation and this is the formulation. Yes, different from what we said, but nevertheless valid in principle'. That has not been done. And that, we say, has, with the greatest of respect, fundamental consequences for the credibility of the case, even to the extent that there were any strands of credibility existing in relation to it.*"

74. The priority aspect of this case falls to be decided by reference to Delaware law and in this regard I am confronted with the Common Delaware Evidence, I reiterate the Paragraph 10 point, and I therefore must respectfully reject the logic of the last-quoted text.

16. Plausibility

75. Having completed his opening submissions on priority, counsel for Teva turned next to the issue of plausibility. In essence, Teva's (successful) plausibility claim is based on its contention that the patent is invalid because the specification did not make it plausible that apixaban would have any useful Factor Xa inhibitor quality. Teva's contention is that, due to lack of plausibility, the claimed invention made no technical contribution to the art and was, therefore, both lacking an inventive step and insufficiently disclosed. The evidence and case-law pertaining to plausibility is considered at some length later in this judgment and I do not, therefore, propose to consider that evidence or case-law at this juncture.

17. Common General Knowledge (CGK)

76. The concept of CGK was described by Charleton J in *Glaxo Group Ltd & Patents Act 1992* [2009] IEHC 277. There, the petitioner, Ivax International B.V., brought proceedings to challenge an Irish patent for an asthma medicine, commonly called Seretide. The patent was held by Glaxo.

Charleton J. concluded that the impugned patent should be disallowed under s.58 of the Patents Act 1992, as amended, because the subject matter of the patent was not patentable in that it did not involve an inventive step. In his judgment, Charleton J. observes as follows, at §43:

> "*The common general knowledge is the technical background of the notional man in the art against which the prior art must be considered. This is not limited to material which he has memorised and has at the front of his mind. It includes all that material in the field in which he is working which he knows to exist, which he would refer to as a matter of course if he cannot remember it and which he understands is generally regarded as sufficiently reliable to use as a foundation for further work or to help understand the pleaded prior art.*"

77. As mentioned previously above, there have already been parallel proceedings between BMS and Teva in England: see *Sandoz Ltd v. Bristol-Myers Squibb Holdings Ireland Unlimited Co* [2022] EWHC 822 (Pat), as affirmed on appeal in [2023] EWCA Civ. 472. (Some weeks after I reserved my judgment in this matter, I was advised by the parties that the UK Supreme Court has recently declined to hear an onward appeal from the just-mentioned decision of the Court of Appeal. So the judgment of the Court of Appeal represents the final limb of the parallel UK proceedings.) The agreed CGK for the purposes of these proceedings is much the same as that set out in Annex A to Meade J.'s judgment in the English High Court proceedings. Given that this is already a long judgment it seems best just to provide the reader with the BAILII link to same: *https://www.bailii.org/ew/cases/EWHC/Patents/2022/822.html* (see Annex A).

78. Counsel for Teva in the course of his opening submissions brought my attention to a number of the paragraphs in the Annex A document. I do not see that there is much benefit to making a long judgment longer by quoting those paragraphs here. I have read the entirety of the Annex A document and simply list below those segments of same to which counsel for Teva drew my especial attention. (The paragraph numbers that I use are those which appear in the Annex A document):

[1] Thrombosis.
See §§123-127.

[2] The Coagulation Cascade.
See §§128-134.

[3] Factor Xa.
See §135.

[4] The Need for a New Generation of Anticoagulants.
See §§164-166.

[5] Serine protease inhibitors.
See §§167-174.

[6] Assays for coagulation inhibitors.
See §175.

[7] Initial testing using a chromogenic assay.
See §§176-177.

[8] Potency.
See §§178-182.

[9] Pharmacokinetics.
See §§196-198.

[10] Enzyme Inhibitors.
See §§218.

[11] Competitive and Non-Competitive Inhibitors.
See §§219-223.

[12] Selectivity.
See §§225-226.

[13] Structure-Activity Relationships.
See §§240-241.

[14] Overview of factor Xa inhibitors in development at priority date.
See §§248-253.

79. As Meade J. states of the agreed CGK document in his judgment in *Sandoz Ltd v. Bristol-Myers Squibb Holdings Ireland Unlimited Co* [2022] EWHC 822 (Pat) (at §78), "*I invite readers of this judgment to read it and then resume* [reading] *here, but for the benefit of those already familiar with the basics of proteins, enzymes, enzyme inhibitors, and drug discovery/medicinal chemistry, they may wish to pass quickly* [on]."

80. I should note in passing that the CGK in this case extends beyond that which was agreed before Meade J. I note also that (i) Dr Gallagher (who gave expert evidence on pharmacology) substantially agrees with the evidence given by Prof. Morrissey (and *vice versa*) and, (ii) for what it is worth (as explained later below I consider that the skilled team is confined to a medicinal chemist and a pharmacologist and does not include a pharmacokineticist) Dr Wargin substantially agrees with the evidence of Prof. Taft (both pharmacokineticists). As a result I am essentially free to take the pharmacology and pharmacokinetics background material as contained either in the document containing the agreed CGK or in the reports of the relevant witnesses.

18. Some Elements of the Patent Application

81. Counsel for Teva turned next to do something of a 'whistle-stop tour' of some aspects of the patent application. Rather than summarise his observations in this regard, it is perhaps more helpful to quote them (though it is important to remember that what is being put across in this quote is Teva's reading of the patent, which does not fully accord with BMS's reading):

> "*Firstly, the field of invention is set out and it's described. Then the background to the invention - this is on page 1. Page 6 describes facets that are desirable and preferable to find in compounds, just a list of them, of desirable matters....*
>
> *The first line, sorry, on page 6 – line 6:*
>
> > 'Efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders.'
>
> *So they're advancing, obviously, the therapeutic elements. And that, of course, they don't make plausible. Then over the page on 7, the top paragraph again:*
>
> > 'The present invention provides novel lactam-containing compounds and derivatives thereof that are useful as factor Xa inhibitors or pharmaceutically acceptable salts....'

That's another reference to it. And then there's a detailed prescription [sic description?] *of the preferred embodiments, beginning on page 8. And you can see a list of the compounds that are identified. If you could go briefly to page 22, I just want to draw your attention, you will see there is a definition of G, which is relevant to another formula. G, at the bottom of page 22, line 26* [in fact p. 23]. *And over the page you'll see it comprises ring D and ring E. And over the page:*

> 'Ring D, including the two atoms of Ring E to which it is attached, is a 5-6 membered ring consisting of: Carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O and S(O)p.'

So, if you go back and look at the ring that is shown on 25 and then E is substituted with 0-2R and there are 0-3 ring double bonds. So, you see this is a definition of G that encompasses a huge range of compounds and molecules that can be attached to those compounds, or atoms that can be attached. Then if you go...to page 68, you'll see embodiment 7:

> 'In another preferred embodiment, the present invention provides a novel compound, wherein the compound is selected from.'

And you'll see the various constituents of the compound. It's a Markush structure, so it is very broad. Then you'll see P4, where you have that in the formula, is G. And G then is the various other substituents that you can include as part of that particular compound. So, that's why, while there are a limited number of embodiments, the range of compounds which this patent purports to embrace, as I said, runs into billions. At the bottom of page 70, line 35, there is the formula for apixaban. But it's given no particular prominence, it's just one of an endless range of compounds that is included in this patent application. In page 143 there's an explanation of the synthesis process and how the compounds can be prepared. Then at 168...you have 'Utility'. And it says:

> 'The compounds of this invention are inhibitors of factor Xa and are useful as anticoagulants….'

So, this is an assertion, it's a reference generally to the compounds and it purports to set out what they can do by way of assertion. Then over the page at 170 [in fact, p.169] *at line 22:*

> 'The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate.'

That's precisely what's already in WO131. In 170 there is something which you'll see referred to in the judgment [*in* Sandoz Ltd *v.* Bristol-Myers Squibb Holdings Ireland Unlimited Co *[2022] EWHC 822 (Pat)*]*....So, I read, or I directed your attention to this yesterday; compounds tested have their preferred compounds, their more preferred compounds. But the important part of that section, which begins on line 20, is that which begins on line 28:*

> *'*Using the methodology described above, a number of compounds of the present invention were found to exhibit'" -*potency levels*- – '"of less than or equal to 10 micromolars.'

That was the level of potency – that's micromolars – that was the level of potency that was being identified. And those were the only ones that were identified by way of a test using the methodology. The others are desiderata, they are an identification of what

you require, but that level of potency is not sufficient for any effective therapeutic agent and what would be required is nanomolar potency, or Kis. Then if you go to 171, there's a reference - we've had Factor Xa, now there's a reference in line 31 to:

> 'Some compounds' - again not identifying them – 'of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. In vitro inhibition constants were determined by the method described.'

Over the page at 172, you will find in line 18:

> 'Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a Ki of less than 10 micromolars.'

Again, way off being effective in terms of potency. Then...the only reference to other utilities, other than as a therapeutic agent that is made and sought to be relied on, it appears, in this case - it was in England - is on 179 of the patent. And you'll see:

> 'The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate to a series of solutions containing test sample and optionally one of the compounds of the present invention.'

And it goes on then on line 6 [p.180]:

> 'Compounds of the present invention may further be useful as diagnostic agents and adjuncts.'

I draw attention to that because that is a more confined use they seek to rely on to sustain the patent....Then the various examples...are given. And Example 18 is the apixaban compound, but it's just one of the many examples that are included. And then 140 examples later on page 298. And then you'll see for the notation of example 140, you'll see the various compounds in table 1 and then the key for the various constituents of those compounds. So, G there stands for methoxyphenyl.

Then the claim in the application is to be found in 316. And claim 1 is just a compound formula, P4/M4. That's a Markush formula and could include almost anything. And the claims in 1 to 15 correspond to embodiments 1 to 15. And if you continue, you'll get all of the claims and you'll find at the end there's 438 pages, as I mentioned. And nowhere does this application make plausible the therapeutic effect contended for with reference to Factor Xa."

19. The Judgment in *Sandoz*

i. Overview

82. In *Sandoz Limited and Teva Pharmaceutical Industries Ltd v. Bristol-Myers Squibb Holdings Ireland Unlimited Company* [2022] EWHC 822, the apixaban battle was fought in the English courts. There, Meade J. held that the apixaban patent as a matter of English law was invalid for lack of plausibility.

83. I turn below to the various paragraphs of the judgment of Meade J. to which my attention was

drawn. Before doing so, I note the following cautionary note in the written closing submissions of BMS, which I respectfully adopt, and which might usefully be stated at this juncture.

> "*At...*[§172 in his judgment for the Court of Appeal in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ltd v. Boehringer Ingelheim Pharma GmbH & Co. KG* [2022] IECA 58, Collins J.] *made the following important comment* [in the context of plausibility]*:*
>
> > *'Doubtless, the issue of whether a claimed technical contribution is plausible is context dependent. Much will depend on the nature of the invention, the nature and breadth of the claimed technical contributions, the disclosure in the specification and what is the relevant common general knowledge.'*
>
> *...That comment reinforces the point that everything depends upon the facts of each individual case. Consequently, 'the particular turn of phrase' used to embody the test for plausibility will, as Collins J noted, be affected by the relevant facts and differences between the formulations used by different tribunals are not significant. Many of the cases in which the issue of plausibility has arisen concern factual circumstances far removed from those of the present case. Whilst the principles laid down in the authorities are obviously important, they do not constrain the court's approach to or assessment of the present facts* [*i.e. the facts in the present case*]."

84. Flowing from the foregoing, I cannot but respectfully note in passing that in its closing submissions, Teva does occasionally stray into offering purported points of law which, on examination, turn out to be arguments by analogy with the facts of other cases. That, with every respect, is not a proper deployment of case-law in the context of patent law proceedings. As Lord Sumption made clear in *Warner-Lambert*, and indeed as Collins J. made clear in *Boehringer*, patent law cases are acutely fact and context-specific. The facts of two cases in relation to a scientific or technical development are extremely unlikely to be the same. Each case must, therefore, turn on an analysis of its own facts. The problem for BMS is that despite my having proceeded so, it has lost on the plausibility point, just as it lost in London, albeit on different evidence.

ii. Plausibility Established by Theory

85. In his judgment, at §40, Meade J. observes as follows:

> "*The first part of this contention was that there is no requirement as such that a patent must contain efficacy data because plausibility can be established by a theory, in particular a theory based on the structure of a compound (or class of compounds). I agree with this, and in itself I do not think the Claimants disputed it. When I come to the facts I will therefore have to assess whether there is a theoretical basis for the plausibility of apixaban arising from structure.*"

86. Teva maintains in this regard that (i) there is nothing in the patent which points to any structure that provides the theoretical basis, and (ii) even if there was some indication of a structure, there is nothing to identify the particular structure that has the efficacy.

iii. *BMS/Dasatinib*

87. At §§44-45, Meade J. observes as follows:

> "44. *BMS argued that* [Case T-0488/16 *Dasatinib/BMS* (ECLI:EP:BA:2017:T048816.20170201)] *...showed that one of the factors that the TBA considered in assessing plausibility was the availability of tests.*

[In Case T-0488/16 *Dasatinib/BMS*, the patent proprietor lodged an appeal against a decision of the opposition division revoking European patent No, 1 169 038 (which was concerned with an anti-cancer compound, datasinib). The opposition division decided that the subject-matter of the main request was not sufficiently disclosed because it had not plausibly been demonstrated at the filing date that the compounds of the invention were protein tyrosine kinase inhibitors suitable for the claimed use, *i.e.* cancer treatment. According to the opposition division, this lack of disclosure could not be remedied by post-published evidence. In its decision, dismissing the appeal, the Technical Board of Appeal noted, amongst other matters, as follows:

> "4.6.2 *....In the board's opinion, the skilled reader can be expected to react in a way common to all persons skilled in the art, which means that any acceptance as to whether or not a particular assertion is correct must be based on verifiable facts, be it information provided in the patent application or available to the skilled person as common general knowledge. In the present case, no such verifiable facts exist. The situation is further aggravated, taking into account that, contrary to the appellant's view the skilled person is not in a position to readily verify the assertion on p.50 in the absence of any detailed information as to the conditions under which the assays are to be carried out.*"

also later observing as follows:

> "*4.9* .... *It is...*a conditio sine qua non *that it is shown that the technical problem underlying the invention was at the least plausibly solved at the filing date. If...the nature if the invention is such that it relies on a technical effect, which is neither self-evident nor predictable or based on a conclusive theoretical concept, at least some technical evidence is required to show that a technical problem has indeed been solved. In the board's judgment, it is not acceptable to draw up a generic formula, which covers millions of compounds, vaguely indicate an 'activity; against PTKs and leave it to the imagination of the skilled reader or to future investigations to establish which compound inhibits which kinase and is therefore suitable to treat the respective diseases associated therewith*."]

In fact, what the Board referred to was the lack of availability of any CGK tests for verifying the assertion in question, and its statement was that that 'further aggravated' the lack of plausibility arising from the specification. In complete isolation from any context I can see how

BMS might argue that it could be inferred that tests could theoretically have a role, but in reality that is plainly not what the Board was saying. I note that BMS/Dasatinib *was referred to by Lord Sumption at [24] and although he referred to a different paragraph in the decision (4.9) he was dealing with the issue of post-filed data, so this too is a reason to reject BMS's reliance on the decision.*

45. In my view my analysis of plausibility should be firmly guided by the points in [37] of Warner-Lambert and by the principle laid out by that case that a contribution by the patentee that is in the specification is needed. The latter is important because, as I hope will become clear when I address the facts, in very large measure, if not entirely, BMS's case for plausibility arises not from anything in 652 but from matters which it contends were CGK. CGK is not BMS's contribution."

88. Meade J.'s regard to the judgment of Lord Sumption in *Warner-Lambert Co LLC* v. *Generics (UK) Ltd* [2018] UKSC 56 is a precise echo of what the Irish Court of Appeal did in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ltd* v. *Boehringer Ingelheim Pharma GmbH & Co. KG* [2022] IECA 58.

iv. Identification of New Compounds Without Use Not Meaningful Invention

89. At §§59-62, under the heading "*Identifying what it means to 'work'*", Meade J. observes, amongst other matters, as follows:

"*59. As I say, the arguments in the case before me on this issue were more complex than those which arose in Fibrogen . In particular, the arguments before me covered the issues of how to address a situation where the specification makes multiple statements of utility, and how to address the situation where the specification makes an assertion of a technical advance which turns out to be overstated.*

60. The Claimants relied on Pharmacia v. Merck [2001] EWCA Civ 1610 . That was a classical insufficiency case about compounds useful as anti-inflammatories. Two potential effects of the claimed compounds were under consideration: their ability to have an anti-inflammatory effect and their ability to be "Cox II selective" which would imply that they did not cause gastric problems. The claims were claims to classes of compounds as such and did not recite any particular use.

61. The defendants had done experiments to prove that compounds within the classes claimed were inactive as anti-inflammatories and lacked Cox II selectivity. One of the patentee's arguments was that it did not matter if the compounds were not Cox II selective as long as they were active anti-inflammatories. The patentee also argued that the invention of a compound claim was the compound as such and that activity was not required.

62. Aldous LJ, with whom Sedley LJ and Arden LJ agreed (the latter giving some additional concurring reasons), roundly rejected the notion that there could be a meaningful invention just in identifying new compounds without any use (see e.g. [61]), and of course that is consistent with Agrevo , Warner-Lambert , Fibrogen and other cases in this jurisdiction and in the EPO. He also held, at [20] and [26] in particular, that based on construing the specification the skilled reader would have identified the invention as the provision of compounds which were both anti-inflammatory and gastric-sparing by reason of Cox II selectivity."

v. Teaching Multiple Independent Utilities for New Compound

90. At §69, Meade J. observes as follows:

> "*I record that the Claimants accepted that where a specification teaches multiple independent utilities for new compounds a patentee may be able to meet an allegation of lack of technical contribution/plausibility by making good only one of them but said that in the present case the teaching in the specification was cumulative; that the non-therapeutic applications were premised on apixaban having the necessary qualities for a therapeutic and meeting further requirements.*"

91. Counsel for BMS drew my particular attention to the observation that "*the non-therapeutic applications were premised on apixaban having the necessary qualities for a therapeutic and meeting further requirements*".

vi. Factor Xa activity as comparator for better compounds

92. At §§74-76, Meade J. observes as follows:

> "*74.* *BMS argued that no particular level of biological or therapeutic activity is required by law when it comes to plausibility. It based this submission on [14] in* Eli Lilly *v.* HGS *(*supra*). I do not believe the Court of Appeal was making any such general statement in that case.*
>
> *75.* *The reason for BMS's making this point was to lay the ground for a submission that any level of factor Xa activity would be good enough, even if it could not achieve anything of known utility, because it could serve as a reference point. So, BMS would say, even if 652 only rendered it plausible that apixaban had trivially low factor Xa activity, it could serve as a comparator for better compounds.*
>
> *76.* *While recognising that patent specifications do not have to reach a standard of excellence or perfection, and a 'working prototype' will often be good enough, there comes a point where activity loses any practical meaning and I think this argument goes beyond that point. In my view the law requires a technical contribution of some, even if low, real significance. There is no contribution in disclosing a uselessly low degree of activity so that comparisons can be made with something which is useful. BMS's argument on this point is not really different from the sort of nihilistic argument that novel compounds with no known use can be put into service as ballast, or the like.*"

93. A couple of points might be made in this regard. First, as I understand Meade J.'s observations at §§74-75, they are to the effect that any level of factor Xa activity would be good enough because it could serve as some form of comparator for better compounds. Second, of note in §76 is the observation that the "*the law requires a technical contribution of some, even if low, real significance.*"

vii. Disclosure of structure and plausibility

94. At §§95-96, under the heading "*Predictability of* in vitro *and* in vivo *characteristics from structure alone*", Meade J. observes as follows:

> "*95.* *It is the business of medicinal chemists to relate structure to activity; they do make predictions based on structure and on knowledge of existing compounds' characteristics, but their confidence in those predictions varies greatly. I agree with BMS's observations in their written closing argument, where they contrasted Dr Redshaw's statement that a 'prediction' as to*

factor Xa inhibition based on structure alone was impossible with Dr Camp's statement that an 'educated assessment' (about apixaban) could be made. BMS said that the statements were not necessarily inconsistent, because for Dr Redshaw a 'prediction' might simply imply a high degree of confidence whereas for Dr Camp an 'educated assessment' would imply a lower one.

96. In my view it was CGK that structure could be a useful pointer in relation to activity but its importance was extremely context dependent. How useful structure is in the present case has to be looked at with all the facts, and I do that below."

95. As I understand Meade J's observations they comprise his response to the notion that a mere disclosure of structure would see the plausibility test satisfied.

viii. Compound as Common General Knowledge

96. Turning to the issue of compounds as part of common general knowledge, Meade J,. observes as follows, at §111:

"*It is worth articulating what I mean when I say that a compound (or series) was CGK in this context. I believe my understanding is also what the parties intended in their submissions. This was a field where the understanding of factor Xa inhibitors and their modes of binding and the dependency on structure was developing but incomplete. Work was building up by accretion and was reflected in the sort of review articles I have referred to above. But no compound had been approved as a drug. So for a compound to be CGK means that it was a widely known compound recognised to have a significant place in the developing knowledge in the field. It does not imply perfect understanding of the compound's binding or that the compound was likely to make an active substance in a drug. This point has some significance in relation to, for example, BMS's deployment of the Lilly series in relation to the 4-methoxyphenyl point on the argument for plausibility based on structure.*"

ix. The Teaching of 652

97. Turning to the substance of 652, Meade J. observes, at §§118-119:

"*118. There follows (page 6 lines 6-35 and especially the list (a) to (g)) a passage to which much importance was attached by BMS at the start of the trial and was the reason why it sought and obtained permission for a DMPK expert….*

119. BMS's case was that the matters (a) to (g) were in some way a disclosure relating to the beneficial qualities that had in fact been achieved by compounds of the invention generally and apixaban in particular."

98. Meade J. continues, again at §119:

"*In my view however it is clear that (a) to (g) are just a generic checklist of things it would be desirable to achieve and have no relation to anything actually demonstrated. The fact, as shown in cross-examination of Dr Taft, that the same language is to be found in other patent applications emphasises and supports this conclusion but is not necessary to it. Although Dr Taft stoutly maintained his evidence, BMS gave up on this part of its case and I need say no more about it.*"

x. Embodiments

99. Dealing with the various embodiments, Meade J. notes, at §126, that "*Embodiment 8 is a list*

of 74 individual compounds. Apixaban is the last on page 69".

xi. Thrombin

100. At §§131-132, Meade J. observes as follows:

> "*131. Much more importantly for my purposes, from page 168 there is a section entitled 'Utility'….*
> *132. There follows some general description of thromboembolic disorders and their causes, and then there is the following statement:*
>
> *'The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin'.*"

101. I note that thrombin is different from Factor Xa and inhibiting thrombin is not at all as effective in preventing clotting.

xii. Testing and Utility of Compounds

102. At §§135-136, Meade J. observes as follows:

> "*135. Experimental details and an explanation of the calculation of Ki are then given and which I need not quote….*
> *136. In my view, the only statement of work actually done is that 'a number of compounds' were tested and had a Ki of 10 μM or less. The statements about lower Kis for preferred/more preferred/still more preferred compounds are aspirational targets, and the statement that the utility of 'the compounds of the present invention' was confirmed is an assertion that an inference can be drawn from the tests that were done.*"

103. At §148 *et seq*, Meade J. looks at the claims of the patent before moving on to the evidence and arguments on plausibility, observing, amongst other matters, as follows:

> "*Evidence and Arguments on Plausibility*
>
> *153. I will break plausibility down into:*
>
> *153.1 Plausibility of factor Xa binding.*
> *153.2 Plausibility of therapy.*
> *153.3 Selectivity.*
> *153.4 Non-therapeutic uses.*
>
> *Plausibility of factor Xa binding*
>
> *154. BMS's case has multiple aspects to it:*
> *154.1 Interpretation of the teaching on page 170 of 652.*
> *154.2 Reliance on the 3g quantity of apixaban made.*
> *154.3 An analysis of the compounds reported in 652 as having been synthesised to show that apixaban was a "typical" compound.*
> *154.4 An analysis based on its structure that apixaban was likely to be an effective factor Xa inhibitor.*
> *154.5 The availability of simple tests to determine the potency and selectivity of apixaban (and other compounds in the Patent) and the fact that they would show positive results. I think this falls into a category of its own and I deal with it separately.*

155. BMS argued that these things taken together mean that 652 makes it plausible that apixaban is an effective factor Xa inhibitor. As I understood it, BMS's case was that that (factor Xa inhibition in itself) was enough for claim 1, but it also relied on it being plausible on the basis of the above that apixaban was useful as a therapeutic for thromboembolic conditions and for the non-therapeutic purposes that I have mentioned above.

156. The Claimants disputed all aspects of BMS's case. A particular focus of their submissions was that the question of plausibility must depend on what was disclosed about apixaban itself and not on 'detective work' directed at inferring what data the patentee had or might have generated but not included in the specification. They also said that:

156.1 Even if the specification of 652 made it plausible that apixaban had been tested and found to have a Ki of the order of 10 µM, that was inadequate for therapeutic use;

156.2 That the non-therapeutic uses needed just as good a level of activity against factor Xa and so were also not plausible and/or were not sufficient in law.

157. Before assessing these arguments, I need to explain in more detail what BMS said about each.

The teaching on page 170

158. Although its written submissions relied on the very general statements in e.g. the abstract of 652, in oral submissions Counsel for BMS accepted that they were not themselves good enough for plausibility and I agree with that, since at most they are bare assertions of utility. So the focus fell on the sentence at page 170 lines 28-32.

159. Counsel for BMS submitted that although it was not explicitly stated which compounds were tested, the skilled reader would assume that all the synthesised compounds, or at least the vast bulk of them, had been tested. The basis for this was said to be that 652 described the invention as being about lactams, that the patentee could only have tested compounds that were actually made, and that there was no point making them unless they were going to be tested.

160. Counsel for BMS did however accept that the skilled reader would infer that not all the compounds tested would have been successful; some might have failed. I agree with this.

161. In my view BMS seeks to read far too much into the sentence. On its own it would not be understood as standing with any reliability for anything more than it says, which is that some unidentified compounds had been tested with activities at the level indicated, and that utility for some broader class (i.e. broader than just the ones tested) could, in the patentee's opinion, be inferred. What that broader class might be cannot be worked out, both because of the lack of detail and because of the inherent ambiguity in the expression 'compounds of the present invention' in this sort of specification where many different Markush formulae are given. [There is an echo in this of Case T-0488/16 (*Dasatinib/BRISTOL-MYERS SQUIBB*)].

162. Further, there is no way from this sentence alone to draw any sort of inference about any individual compound, be it apixaban or any other. There is simply no information, and given Counsel for BMS's acceptance that some compounds might also have failed, there is no way for the reader to know of any particular compound whether it was good or bad.

163. To be fair, I do not think that BMS really seriously maintained a case that the disclosure on page 170 was enough on its own. It therefore sought to tie it to apixaban by means to which I will now turn.

3g quantity of apixaban

164. As I have already said, apixaban is Example 18 in 652 and at page 222 line 25 it is identified that 3.07g was ultimately made. Although the Claimants raised some minor questions about the reporting of the quantities reported in the stages of the work I did not think they undermined the conclusion that of the order of 3g was made.

165. In addition, I find that that was the most of any compound reported to have been made in 652, by some distance.

166. There is no explicit disclosure of why the patentee made that amount. BMS said that the reader would infer that it was because early results had been favourable and the patentee wanted to take work on the compound forwards. The evidence of the DMPK experts (this was an isolated instance where their evidence was relevant) was that this was possible, with the further work intended being, possibly, second species pharmacokinetics or early toxicology.

167. The Claimants responded that there were other possible reasons, such as making apixaban as an intermediate on the way to making something else (although Dr Redshaw could not make any concrete suggestion) or as a thrombin inhibitor, which seems possible given the teaching of 652 on that topic, if not especially likely.

168. In cross-examination Dr Camp was taken to a 2003 publication by Scott Sheehan of Lilly ('A four component coupling strategy for the synthesis of D-phenylglycinamide-derived non-covalent factor Xa inhibitors') where a similar large amount was made of a compound which was not successful. He accepted on the basis of it that the amount of a compound made could not be taken as an indicator of success in every case; one possibility was just that 'the chemistry worked better'.

169. There was, Dr Camp accepted, no evidence in any of the CGK review articles of the authors selecting compounds for review or inclusion based on the amount made.

170. In her oral evidence, Dr Redshaw maintained her overall position that judgments could not be made about a compound's qualities from the amounts made.

171. The 3g point is not completely without relevance. It is a point which, unlike other aspects of BMS's case, is relatively free of hindsight, in the sense that it sets apixaban apart from the other exemplified compounds based on information in 652 itself that I think the skilled reader would notice.

172. However, in its substance it is a very weak point. Lacking any data, one does not know why the patentee made such a quantity and reasons other than factor Xa inhibitory activity are real possibilities. And I do not see how the point can go any further than that the patentee thought that apixaban was promising. A bare assertion to that effect in 652 (bare in the sense of lacking data or reasoning) would not have been any use in establishing plausibility, as is clear from the second point in [37] in Warner-Lambert . But 652 does not even contain such an assertion.

The compounds synthesised; apixaban as a 'typical' one

173. This point needs some explanation before its weight can be assessed.

174. Dr Camp undertook a detailed exercise in which he looked at the compounds listed in embodiments 8 and 15, having particular regard to those which had been synthesised. What he did was to convert the names of the compounds into structures, then worked out which were in one of the lists and which had been synthesised, and grouped them by core structure and by their functional

groups. He looked at which features occurred the most often. The Claimants referred to this as 'frequency of use analysis'.

175. Dr Camp's written evidence was that a medicinal chemist would have undertaken this sort of work and would have been very interested in the results.

176. BMS's position is best articulated in a series of steps. I have based the following on its closing written submissions.

177. First, it points to Embodiment 7 as being the first in 652 to define compounds necessarily incorporating a lactam, with a bicyclic core as follows….

178. Here the lactam of interest is, BMS said, at M4 (there is also one in the core itself).

179. BMS then submits that in Embodiment 7:

179.1 M_4 is defined as A-B which is selected from the following two substituents comprising a phenyl group attached to a lactam (652 at page 68 lines 3-9)….

179.2 P_4 is defined as G (page 68 at line 1) which is itself defined as the group of compounds listed from line 6 of page 57; and

179.3 R^{1a} is defined at page 52 lines 11-12.

180. It is worth mentioning that when it comes to the structural analysis below BMS says that M_4 would be understood to bind in the S4 pocket of factor Xa and P_4 in the S1 pocket, with R^{1a} as part of the scaffold.

181. Dr Camp called the lactam on the left side of the two options above 'Lactam 1' and that on the right 'Lactam 7' in an analysis which he then did and which was set out in his exhibit NPC26. NPC26 covers 131 compounds, of which 74 were synthesised (those in Embodiment 8). Rather confusingly, Dr Camp referred to M_4 as R_3, to P_4 as R_2 and to R^{1a} as R_1 in his exhibit NPC26.

182. Once organised in this way it is possible to analyse, Dr Camp said, the pattern of what the patentee did. BMS submitted that of the 74:

182.1 lactam 1 was by far the most common lactam in the M_4 position (42 instances, the next most common, lactam 7, having been used 24 times);

182.2 4-methoxyphenyl was by far the most common substituent in the P_4 position (44 instances, the next most common, 3-chlorophenyl, having been used 6 times); and

182.3 CF_3 was the most common substituent in the R^{1a} position (20 instances, the next most common, carboxamide, having been used 13 times).

183. And it further submitted that the skilled medicinal chemist would realise that apixaban:

183.1 has the most common lactam in the M_4 position, i.e. lactam 1;

183.2 has the most common substituent in the P_4 position, i.e. 4-methoxyphenyl; and

183.3 has the second most common substituent in the R^{1a} position, i.e. carboxamide.

184. This was very elaborate work, and one of its steps involved drawing the compounds starting from their names, so as to be able to identify what core and functional groups they had. The Claimants questioned whether CGK means existed at the priority date to do that, and whether the skilled medicinal chemist would undertake the exercise.

185. The issue of whether the tools existed to draw the structures was an unnecessary digression in my view and in any event I find that at least one software package existed that could do it (ChemDraw 6.0 Ultra), which the skilled medicinal chemist could find if they wanted to do the task.

186. Whether they would want to do the task to the extreme level of detail undertaken by Dr Camp is doubtful, in my view, but one has to bear in mind that Dr Camp was doing it in the crucible of litigation, where he had to take a rigorous approach given his obligations as an independent expert and

because anything he said would be picked over most assiduously by the Claimants.

187. I accept Dr Camp's evidence that the general scheme of what was done by the patentee and the compounds chosen for synthesis in terms of the patterns of structures could be identified with significantly less effort than went into NPC26. I also accept his evidence that with that lesser effort it would be appreciated, if apixaban were considered, that it was fairly typical, in the sense of using a core and substituents common to quite a large number of the compounds that were synthesised.

188. However, the utility of the analysis is quite another matter. I do not think there was any evidence that it was CGK to use this kind of frequency analysis to work out which compounds from a broad range were active, or promising. A crucial point to appreciate is that the analysis was done without any biological data to ground it. Dr Redshaw said, and I accept, that she had never analysed a set of compounds like this for which there were no biological data, and that there were many reasons why particular substituents might be frequently used, not just activity.

189. Dr Camp accepted in essence that lacking biological data the skilled medicinal chemist would not have done this sort of exercise and that the exercise was 'just really understanding the issues that they [the authors of 652] are trying to resolve'. So he retreated a long way from his written evidence.

190. Even taking this analysis along with the indication from page 170 of 652 that some positive results existed does not help BMS. One simply cannot infer which if any of the 74 compounds had good biological results, which had bad results, and which had no results. Nor can one infer whether the 'typical' compounds all behaved the same, or similarly. As Counsel for the Claimants put to Dr Camp at one point, this is SAR (structure-activity-relationship) analysis without any 'A'.

191. The Sheehan paper to which I have referred above in relation to the 3g point was again put to Dr Camp on this part of the case. He accepted that it showed 25 compounds with a particular structural feature having been made, with consistently unpromising results. This supported the Claimants' position for similar reasons. Again, and as with the 3g point, Dr Camp did not identify any of the review papers from the factor Xa inhibitor art deploying frequency of use to identify promising compounds.

192. I also thought that Dr Camp's oral evidence illustrated that this part of BMS's case was artificial in working backwards from apixaban specifically, and the later knowledge that it is indeed a potent factor Xa inhibitor. This was apparent from his explanation of his earlier involvement in the Canadian case, and the analysis in relation to R^{1a}, where apixaban has a carboxamide, which is not the most common substituent.

Structural analysis

193. This is the most complex part of BMS's case and understanding it and explaining it is not assisted by the varying and different ways in which the parties developed and organised their cases.

194. As it seemed to me, BMS's position had the following key elements:

195. First that the skilled team would have known from the CGK of the crystal structure of factor Xa that binding in the S1 and S4 pockets was very important. I have accepted that when dealing with the CGK.

196. Second, that DPC-423 was a very well-known compound in the CGK with good activity. That was also common ground.

197. Third, that based on a comparison with DPC-423 and/or in the light of the common general knowledge, the structure and individual groups in apixaban made it plausible that it would be effective in binding to and inhibiting factor Xa. Both sides referred to the following comparison of DPC-423 and apixaban….

198. The Claimants submitted that DPC-423 was so different that it would not be called to mind at all when considering 652, but this comparison at least provides a way to organise the topics which need considering in relation to the structural argument. The topics of relevance are:

198.1 Apixaban has a 4-methoxyphenyl in the P1 position where DPC-423 has a 3-benzylamine.

198.2 Apixaban has a lactam at the P4 position where DPC-423 has a methylsulfonyl benzene.

198.3 Apixaban has a bicyclic core where DPC-423 has a monocyclic core. BMS called this apixaban's 'rigidified' core.

198.4 Apixaban has a carboxamide attached to the pyrazole ring (circled in orange) where DPC-423 has a trifluoromethyl.

199. I will deal with the points in that order. It was common ground that the additional fluoro group ringed in yellow was unimportant.

200. In his oral evidence, Dr Camp outlined a still more complex analysis which he called the 'direction of travel' and which embraced 131 and other matters. BMS did not defend this.

[I note that while there were various mentions of 'direction of travel' before me, this notion gets no mention in the oral or written closing submissions of BMS. Nor do I understand BMS to be making such an argument any longer. If this line if argument is being made, the point arising is – to borrow from the opening submissions of counsel for Teva – that (i) the skilled addressee of WO652 would be aware that DuPont had developed DPC-423 and that DuPont had also filed WO131, and hence (ii) WO 652 would be viewed as the continuation and refinement of their work. This line of argument was, I understand, abandoned in the United Kingdom as not legitimate. So for it to be raised now, in Ireland (if it is being raised and whatever about BMS's opening submissions, there is no suggestion in its closing submissions that it is), that would yield that "*disquieting*" shift of position in different jurisdictions to which Collins J. refers in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ltd* v. *Boehringer Ingelheim Pharma GmbH & Co. KG* (at §184) when dealing in that case with the stance adopted by Boehringer in Ireland and the Netherlands.]

P1 4-methoxyphenyl

201. There are two main strands to this point. The first is whether there was a basis in the CGK for this substituent as a S1 binder. The second is whether the chemistry of it would provide a basis for thinking it would be beneficial, or not.

202. The CGK basis relied on by BMS was the Lilly series identified above. I have held that they were CGK and that so was a more general move towards neutral binders at the P1 position. However, the fact that the series was CGK does not mean that it was well understood. Dr Camp's written evidence said that its binding mode was unclear, and in his oral evidence he agreed that one of the review papers (Rai) did not regard the 4-methoxyphenyl as being the P1 element/S1 binder. Other of the review papers (Ries, Betz) proposed replacing the 4-methoxyphenyl group, and Maignan & Mikol expressed the same view.

203. Confronted with these papers, Dr Camp's evidence was ultimately to the following effect (T4/319):

> *Q. Having looked at this Lilly series, and what it is said about it, there was no oral bioavailability data as you agree, I suggest in the light of that, this Lilly series would not have been regarded by the medicinal chemist in 2001 as being a key series of inhibitors?*
>
> *A. I think it is more just the groups, you know, the neutral S1 binder. I mean, clearly the Lilly series here is not very well optimised. I can just tell that looking at the structures. So I think it is more the fact it has a neutral S1 binder.*
>
> *Q. In fact, in this…series…we do not know what binds in S1 and what binds in S4, do we?*
>
> *A. Not only based on modelling predictions, obviously it is a weakly active compound and it has the same group, so I agree it is not clear.*
>
> *Q. No. If you had read what these papers have said about this series, the medicinal chemist would not have had in mind the para-methoxyphenyl group as being a successful binder, would he?*
>
> *A. Not based on this series.*

204. So I reject the P1 4-methoxyphenyl case based on the Lilly series. Not only was the series not well optimised, but it was not even clear which way round it bound (it was agreed to be CGK that this kind of S1/S4 'flipping' was possible). Also, when being asked about the DPC-423 comparison more generally Dr Camp said that the Lilly series was "totally different" and not comparable, and I found this very hard to square with his relying on it for the 4-methoxyphenyl group.

205. As I have mentioned above, the DuPont series also relied on in this connection by Dr Camp in his written evidence was not CGK, and there were no data for it; BMS did not rely on it.

206. Further, when he was asked about a direct comparison between DPC-423 and apixaban at the P1 position, Dr Camp accepted that while the benzylamine at the 3 position in DPC-423 could form a salt bridge with Asp189 at the base of the S1 pocket, the 4-methoxyphenyl in apixaban could not. In this context he said that it was "very, very hard" to make a prediction, that it was not obvious why the 4-methoxyphenyl group would go in the S1 pocket and that from a structure-based design perspective it was 'very unusual' that (as we now know) it did. He said 'I do not think you can really rationalise it' and it was an unexpected finding. See T5/505-507.

The lactam at the P4 position

207. Dr Camp had summarised his views on this point at paragraph 4.1 of his second report. One matter on which he and Dr Redshaw agreed and which he mentioned there was that the S4 pocket allowed for a degree of variability (was "catholic" as Dr Redshaw put it in oral evidence). While that helps BMS to some extent it does not mean that any group would be regarded as a plausible binder at that location.

208. Other of Dr Camp's points in paragraph 4.1 were significantly undermined in cross-examination. In particular it turned out there was no CGK basis for 4.1(c) and the examples he had given did not support 4.1(d). When he was

asked in general terms about the lactam (at T5/518) there was the following exchange:

> *Q. What I would suggest to you, doctor, having looked at your reasons for saying that the medicinal chemist would expect the lactam to bind in the S4 pocket, I suggest that there is absolutely nothing here to support that conclusion and the medicinal chemist would not, based on his common general knowledge, be able to make a reasonable prediction that the lactam group would bind in that S4 pocket?*
>
> *A. I think the lactam has to go in that pocket. It cannot go anywhere else. It is hard to rationalise it, I totally agree, but looking at the binding modes, you know, it cannot go anywhere else. So it has to go in the S4 pocket, and obviously you can test that. You know, this is sort of, in my opinion, well beyond the structure-based design. I think your comments are fair.*

209. What this reflected was that based on the later knowledge that apixaban does bind, one now knows that it must be the case that the lactam group binds in the S4 pocket. But even now it is hard to rationalise and it is well beyond structure-based design. Any possibility that 652 could provide plausibility based on structure is clearly excluded in respect of this group.

The rigidified core

210. In comparison with the two previous points this one was relatively neutral; rigidification of this kind was generally known to be possible and might or might not be beneficial. It would introduce an extra degree of uncertainty in trying to make a prediction from DPC-423, however. There was no positive reason to think it would work and no positive reason to think it would not.

Dr Redshaw's evidence

211. Dr Redshaw's written evidence was that:

211.1 The compounds with 4-methoxyphenyl groups in the review papers would not have been of interest.

211.2 No prediction from the 4-methoxyphenyl compounds could be made, in particular because of the uncertainty of the orientation of binding to which I have referred above.

211.3 Although there was flexibility in the S4 pocket there was no reason to think that the lactam group would bind there.

211.4 There was no reason to think the rigidified core would hold a 4-methoxyphenyl and a lactam group in the right orientation.

212. Counsel for BMS made some progress on the first point and I have concluded that the Lilly compounds were CGK, but Dr Redshaw was not effectively challenged on the other three points and I accept Dr Redshaw's evidence.

The differences in aggregate

213. Taking all three differences from DPC-423, Dr Camp accepted that it was not possible to predict the properties of the synthesised compounds, even the ones with the 4-methoxyphenyl group (see T5/511).

Conclusion on the structure case

214. I find that the overall position is that in relation to the individual points and in relation to their aggregate effect no prediction based on structure could be made from the CGK, and indeed apixaban's binding is unexpected and hard to explain. There is nothing in the CGK positively to say that it could not bind effectively, but that is not the point – there has to be some positive reason to think there might be success.

215. It is also a significant problem for BMS that its case based on structure relies entirely on CGK. It does not draw on anything in 652 at all. So if plausibility were to be based on structure I cannot see how it represents a contribution by the patentee.

Plausibility of factor Xa binding – overall assessment

216. Taking all the above matters together, I conclude that 652 does not make it plausible that apixaban would have factor Xa binding of the level of 10 μM as referred to on page 170, or any useful degree of binding. The fundamental problem is that identified by the Claimants: there is simply no reference to apixaban there to allow an inference that it was one of the compounds for which useful results had been achieved. The frequency of use analysis suffers from the problems identified above and while the reader of 652 would infer that work of some kind had been done on lactams with quite a number made, there is no way to connect any particular compound to any degree of activity. Apixaban had been made in quantity but that does not mean anything for activity, and the structural arguments fail on the facts.

217. So BMS''s points fail individually and their whole is no greater than the sum of their parts. Since there is no plausibility of any meaningful factor Xa binding the Patent is invalid, since all the applications for apixaban depend on factor Xa binding. I will however go on to make conditional factual findings about those applications.

Plausibility of therapy

218. Even if 652 had made it plausible that apixaban had the degree of binding indicated on page 170 (10 μM), on my findings as to the CGK that would not make it plausible that it would be useful in therapy, because nanomolar potencies were needed for that.

Selectivity

219. 652 contains nothing to indicate that apixaban is selective for factor Xa as compared with other serine proteases. As I have indicated above, the Claimants said that this gave rise to an additional lack of plausibility because selectivity is needed in view of the fact that inhibition of other serine proteases may interfere with what would otherwise be a useful effect on factor Xa. The Claimants argued that this is not just about side effects (they accept that a patent does not have to exclude side effects to make therapy plausible) but about efficacy, for the treatment of the thromboembolic conditions in question.

220. However, against that 652 does not promise any such selectivity.

221. In my view, had it been the case that 652 made plausible a level of factor Xa inhibition which could form the basis of an effective therapy, an omission to prove selectivity would not mean plausibility for therapy could not be shown. My reason is that not showing selectivity would only mean that there was a risk of reduced overall efficacy by an off-target effect on another serine

protease. It would not mean overall efficacy was not plausible. The statement in 652 that some activity against other serine proteases might be possessed by "compounds of the present invention", to which I have referred above, does not change the fact that an off-target effect would be merely a possibility.

Clear and easy tests

222. I accept BMS's contentions that it would not have been difficult or burdensome to test apixaban for its factor Xa inhibitory activity, and that if such tests were done a very good level of activity would have been found. The same applies to selectivity and to bioavailability, although I have found above that lack of selectivity data would not lead to a lack of plausibility for therapy, and bioavailability would not be seen as essential since a drug could be given parenterally if necessary.

223. However, the fact that I accept BMS's factual contentions about testing does not help it. In the absence of making some showing of plausibility based on one of the other matters relied on (the teaching on page 170, the 3g point, frequency of use, structure), the ability to test cannot get BMS any further than the patentee in Warner-Lambert . It provides (at a maximum) the sort of encouragement-plus-ability-to-test that the Supreme Court rejected, as I set out above. I say 'at a maximum' because my analysis above means there is not even any encouragement concretely referable to apixaban."

[Counsel for Teva drew my especial attention to this last point, given what he contends to be an attempt by counsel for BMS in the within proceedings to create some fissure between the decisions in *Warner-Lambert* and *Boehringer*. (When I have regard to the closing submissions of BMS I do not see any such effort). Additionally, Meade J. makes what counsel for Teva contends to be the noteworthy point that his analysis shows that there is "*not even any encouragement concretely referable to apixaban*".]

104. Meade J. then turns to non-therapeutic uses, concluding, at §233, that "*BMS's case in relation to non-therapeutic uses would fail on the facts…even if (contrary to my earlier conclusion) the specification of 652 made it plausible that apixaban had some level of factor Xa inhibitory activity as indicated….*"

20. The Judgment of the English Court of Appeal in
Sandoz Ltd v. *Bristol-Myers Squibb Holdings Ireland Unlimited Company*
[2023] EWCA Civ. 472

105. The judgment of Arnold L.J. in *Sandoz* (in which the judgment of Meade J. is affirmed) includes a review of previous case-law of the EPO Boards of Appeal (including a consideration of the decision in Case G2/21 *(Insecticide compositions/Sumitomo* [ECLI:EP:BA:2023:G000221.20230323], at §§43-53) and a useful recapitulation of the consideration of the law on plausibility in United Kingdom case-law (see §§26-42). As I consider relevant case-law of the European Patent Office and also the law on plausibility later below, I do not pause to consider them here.

106. I turn now to the various paragraphs of the judgment of Arnold L.J. to which my attention was drawn (except those which, for the reasons stated in the preceding paragraph I have elected not to consider at this point in my judgment).

107. By way of starter, I should perhaps note that when we reached Arnold L.J.'s observation, at §54, under the heading "*The skilled team*" that:

> "*As the judge recorded at [12], by the end of the trial there was no dispute that the patent was addressed to a skilled team comprising (i) a medicinal chemist and (ii) a biochemist or pharmacologist with relevant experience in industry*",

counsel for Teva observed as follows:

> "*I'm not saying that an issue estoppel arises, but I do say the Court should look very carefully at any attempt to alter the case or alter the presentation to this Court. And that is something that Mr Justice Collins touches on in his judgment* [in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ltd* v. *Boehringer Ingelheim Pharma GmbH & Co. KG* [2022] IECA 58]. *So, to the extent that they seek to adopt a different proposition, that's something that there is no absolute legal bar to doing, but it's something that should be treated with great care and it would have to be very clearly demonstrated, the rationale and justification for doing that.*"

108. Counsel was of course correct: no issue of estoppel arises. However, as I touched upon in chapter 1 (and consider at length in chapter 30), for obvious reasons, weight and respect falls to be accorded by me to the decisions of the neighbouring jurisdiction, largely because the courts of that jurisdiction are applying the same system of patent law and both are common law jurisdictions. That said, I have an obligation to decide the case before me on the evidence presented to me and not on the evidence presented to any other court, whether in the United Kingdom or elsewhere. If the evidence is different, the outcome may be different, albeit that here (when it comes to plausibility – the London court did not have to decide priority – the outcome has proven to be the same).

109. Counsel moved on to bring me to §§89-105 of Arnold L.J.'s judgment. I do not believe that it is necessary to quote those paragraphs. I have read them, I have read the whole of the judgment, if I might respectfully observe it is an informed and helpful judgment, as is that of Meade J., subject to the observations that I have already made about the differences in evidence in the case that was heard by Meade J. and the present case.

21. Some Questions for Me to Answer

110. Counsel for Teva concluded his opening submissions by positing some questions that Teva consider it will be necessary for me to answer when it comes to the issue of plausibility. I consider the law as to plausibility at some length later below and respectfully confine myself in this judgment to answering the questions that the law would have me answer.

C. The Opening Submissions of BMS

111. The opening submissions of BMS can more shortly be dealt with. First, BMS briefly touched upon the decisions in jurisdictions other than the United Kingdom. I consider those decisions in more detail in chapter 30. Second, BMS brought me through the law on plausibility and its application in the present proceedings. I consider the law on plausibility separately in this judgment, and I then apply that law to the facts of the case before me. So I do not consider it necessary to replicate that analysis at this juncture.

III. THE IN-HOUSE EVIDENCE

3

Some Prefatory Remarks

i. BMS Policy

112. One will find a lot of mention in the *viva voce* examination of Mr Brown and in the oral testimony of Ms Leung and Mr Golian, (all BMS employees), of the alleged policy represented by certain emails of October 2001 and/or an internal manual. When Teva's case was being opened on the first day of these proceedings, I was told that, in October 2022, O'Moore J. was told in another aspect of these proceedings that the policy comprised in the emails had been implemented but that it was now known that this is not so, as though there was something untoward in what had happened. Maybe that point would have had more significance in a case where I was not confronted with the Combined Delaware Evidence. However, I am confronted with the Combined Delaware Evidence, that leads to the Paragraph 10 Point and thus I do not consider that I have to examine in detail what was or was not said to O'Moore J.

ii. *Cases T-1201/14 and T-1786/15*

113. BMS has contended in its submissions and it may be right (I do not know) that in making its 'non-implementation of policy' contentions, Teva was seeking to bring this case within the ambit of a line of EPO Board of Appeal authorities, in particular Cases T-1201/14 and T-1786/15 (considered below) in which it sought to rely on a policy as yielding a transfer of a priority right. There is a problem for Teva in making this case: BMS has never sought to rely on a policy simpliciter as yielding a transfer of a priority right. Nonetheless, as a courtesy to Teva, I consider these cases below.

1. Case T-1201/14 *(Transfer of right of priority)* (ECLI:EP:BA:2017:T120114.20170209)

114. The patent proprietor in this case was Innovative Sonic Ltd. So the case is generally known as the *Innovative Sonic* case. Innovative Sonic claimed priority from a US provisional application. The US provisional application was filed by the inventor and assigned to ASUSTeK. Innovative Sonic claimed that there had been a transfer from ASUSTeK by reason of: (a) a *nunc pro tunc* assignment under US law; (b) an implied transfer under either German or Taiwanese law; (c) a direct transfer under US law. In respect of (b) Innovative Sonic had a general policy as to the transfer of new and pending patents between it and ASUSTeK and certain instructions to patent attorneys. The Technical Board of Appeal found that Innovative Sonic had not proven succession in title. In so holding, the EPO emphasised that the policy and instructions had not been consistently followed. However, a critical difference between that case and this is that (as the Technical Board of Appeal notes in its consideration of the proposition that there had been a transfer by virtue of a general policy under German law; the Board decided not to admit the line of argument concerning implicit transfer under Taiwanese law (see §3.2.4.4)) Innovative Sonic submitted that "*By executing...policy the right of priority for the patent in suit was transferred to the appellant*" (§3.2.2). As I have stated above, BMS has never sought to rely on a policy simpliciter as yielding a transfer of a priority right. Its case in this regard comprised the Control Proposition.

2. Case T-1786/15 (*BMP Antagonists/General Hospital Corporation*) (ECLI:EP:BA:2020:T178615.20201015)

115. The patent proprietor in this case was The General Hospital Corporation. So, the case is generally known as the *General Hospital* case. There, the employee-inventors were the applicants for the provisional application from which the patent claimed priority. The General Hospital

Corporation filed the Patent Cooperation Treaty application. The inventors were required by D31 (MGH Intellectual Property Policy) to transfer certain IP rights to the Massachusetts General Hospital, the parent company of the General Hospital Corporation. The General Hospital Corporation relied on an internal 'Ownership reallocation policy' (D51) to assert a transfer of priority or equitable title from the parent (the Massachusetts General Hospital) to the subsidiary (the General Hospital Corporation) prior to the PCT application. The Technical Board of Appeal found that the policy did not discharge the burden of proof because it did not provide evidence that it was in fact adopted. Again, even in this description of the facts (which I have respectfully adopted from the written closing submissions of Teva), one can see the problem presenting: the General Hospital Corporation relied on an internal 'Ownership reallocation policy' (D51) to assert a transfer of priority or equitable title from the parent (the Massachusetts General Hospital) to the subsidiary (the General Hospital Corporation) prior to the Patent Cooperation Treaty application. As I have stated above, BMS has never sought to rely on a policy simpliciter as yielding a transfer of a priority right. Its case in this regard comprised the Control Proposition.

116. In the next three chapters of this judgment, I turn to consider what I have loosely styled as the 'in house' evidence before me, namely the evidence of Mr Brown, Ms Leung, and Mr Golian.

4

Viva Voce Examination of Mr Brown

117. Pursuant to my previous judgment in these proceedings (see [2023] IEHC 376) a *viva voce* examination of Mr Brown took place towards the end of Day 2 of the trial. I turn now to consider the *viva voce* examination of Mr Brown.

1. Is the Manual Policy?

118. Asked whether the manual represents BMS policy, the following exchange occurred between counsel for Teva and Mr Brown:

Counsel:	[F]*irstly, do you accept that the manual is BMS policy?...*
Mr Brown:	*I think this is part of the policy, along with what we saw in the emails…*
Counsel:	*I see. I just want a clear answer; is the manual the policy of BMS? We can leave aside whether it's incorporating…. Is it the policy? Does it reflect the policy? ….*
Mr Brown:	*I don't think the manual rises to the level of the policy of BMS.*
Counsel:	*I see. So, the email is the policy; the manual doesn't rise to the policy, is that correct?*
Mr Brown:	*I think the e-mails that we saw, in those e-mails those are the policy that the manual is trying to incorporate….*

2. Who Received the 'Policy'?

119. Counsel for Teva proceeded next to ask who received the policy, at which juncture the following exchange occurred between counsel for Teva and Mr Brown:

Counsel:	[W]*ould you confirm to the Court that it was sent to lawyers as well as paralegals?*
Mr Brown:	*Yes, I agree with that.*
Counsel:	*So, this wasn't just some exchange between paralegals….* *It was clearly addressed to attorneys as well, isn't that correct?*
Counsel:	*It's addressed to attorneys as well, yes.*

3. Duration of the 'Policy'

120. As to the duration of the policy, Mr Brown confirmed that he did not believe that Chapter 13 of the manual was altered until 2005.

4. Differences between the 'Policy' and the Manual

121. Asked by counsel for Teva whether he sees any difference between the policy set out in the e-mail of 24th October 2001, the policy set out in the manual, or the (Lori) e-mail of 30th January 2002, Mr Brown indicated that "*I think it's the same policy, just it includes another sort of bucket of IP of what to do when...you're claiming priority to a provisional prior to October 2001.*"

5. Substance of the 'Policy'

122. As to the substance of the policy, the following exchange occurred between counsel for Teva and Mr Brown:

Counsel:	[In the 'Viva Voce Examination of Scott Brown Book of Documents'] *you say: 'This represented the policy with respect to provisional filings prior to 1st October 2001 and in respect of those, it was the policy that BMS Pharma should apply for the patent.' Is that correct?*
Mr Brown:	*If it's claiming priority to something prior to October 2001, then the name should be in BMS Pharma.*
Counsel:	*That was the policy? It should have been in BMS Pharma?*
Mr Brown:	*If it's claiming priority of something prior to October 2001.*
Counsel:	*And do you know whether the patent in this case was claiming such priority?...*
Mr Brown:	[I]*t claimed priority, yes.*
Counsel:	*But what this was saying is the application should have been in BMS Pharma?*
Mr Brown:	*That's what this is saying, according to this policy it should have been.*
Counsel:	*And that was the policy?*
Mr Brown:	*Yes.*
Counsel:	*And was the policy in this manual implemented?*
Mr Brown:	*Yes, it was.*

123. After this exchange the following exchange occurred between Mr Brown and myself:

Judge:	[I]*f a director said, 'I'd like to know what the policy is in this area, I'm a director I'm entitled to know', you would give the director the emails, is that it?*
Mr Brown:	*Well, I think we would perhaps summarise the emails for her in a comprehensive way.*

124. When I recall how hard-fought the application was that led to my ordering the *viva voce* examination, I respectfully do not see that much was gained by having Mr Brown give the oral testimony that he did. Mr Brown is, if I might respectfully observe, a clearly talented individual; however, the evidence from Ms Leung and Mr Golian was more informative and helpful when it came to the issues that it has fallen to me to decide and to which their evidence relates.

5

The Evidence of Ms Leung

A. Introduction

125. Ms Leung is presently an executive vice-president and general counsel at BMS Company. Between 1999 and 2006 she was corporate secretary of the board. From September 2006 she was corporate secretary and interim general counsel. In February 2007 'interim' was removed from her title and she became corporate secretary and general counsel. She or members of her team are heavily involved in acquisitions and divestitures from a subsidiary management, securities and filing and record keeping standpoint.

126. I turn now to consider the oral testimony of Ms Leung. Subject to para. 4 of this judgment, an abridged version of her written evidence is set out at Appendix 8. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

B. Examination

1. BMS's approach to acquisitions

127. Asked by counsel for BMS about BMS's approach in respect of acquisitions during the course of her employment and whether it has changed, Ms Leung indicated as follows:

> "*The way we handled acquisitions has not changed since the time I joined Bristol-Myers Squibb...I had more visibility into subsidiary management when I became Corporate Secretary in 1999....*[T]*he way we manage acquisition subsidiaries is that we developed and formulated an acquisition sub and all of the assets of the company we were acquiring would go into the acquisition sub. And the acquisition sub was a wholly-owned subsidiary of Bristol-Myers Squibb and it was formed for the purpose to operate in the best interest of Bristol-Myers Squibb Company, BMS Co, the parent company. And that's been our consistent practice in the time I've been at Bristol-Myers Squibb, to the best of my understanding.*"

128. I asked Ms Leung if everything goes into the subsidiary and she indicated that **"***Everything goes in – generally. There may be some instances...where there may be a good business reason to put it in a different sub. But still...it would be a wholly-owned subsidiary of Bristol-Myers Squibb and we would have a complete unfettered and centralised control over that subsidiary.*"

2. BMS Employees as Directors/Officers

129. Asked by counsel about an email that she sent on 24th August 2001 in which she identified various BMS employees who were to serve as directors/officers of various BMS subsidiaries, Ms Leung indicated as follows:

> "*This is one of my responsibilities as corporate secretary. In the context of an acquisition, we would name the directors and officers who were employees of the parent company, BMS Co, to be directors and officers of the new wholly-owned subsidiary that we were forming for the purposes of the acquisition....I know each one of the people who are named here and I can confirm they were all BMS Co employees.*"

130. Brought to another email of 24th August 2001 to Cravath (BMS's external counsel), Ms Leung indicated that:

"*Cravath...represented us in the acquisition, and...were in the process of establishing the new wholly-owned subsidiary under Delaware law. And to form that subsidiary, we needed to identify the names of the directors and officers of the new subsidiary.*"

131. Asked to explain why BMS was replacing or proposing to replace the directors and officers of the subsidiaries it was acquiring, Ms Leung responded as follows:

"[T]*his is a longstanding practice at Bristol-Myers Squibb. As I indicated before, whenever we acquired a company, we'd establish a new sub and...put, as directors and officers of that successor wholly-owned subsidiary, Bristol-Myers Squibb employees, because it was the expectation that everything they do as a director and officer of the sub would be to the benefit of BMS Company. So, these are people who, for the most part and probably in all of these cases, who have served in other wholly-owned subsidiaries of Bristol-Myers Squibb as well.*"

132. Asked to confirm that all of the proposed new appointed directors and officers were employees of BMS Co or other entities, Ms Leung confirmed that she knew each of the individuals and that they were all employees of BMS Co. Asked if, when the transaction completed, they were all duly appointed to the proposed positions, Ms Leung indicated that they were.

3. Dr Rasser's Observations

133. Brought to certain observations made in the statement of Dr Rasser, Ms Leung confirmed her view to be that the (in effect, governance) approach taken by P&G is irrelevant to the situation at BMS. As to her stated understanding in her statement that different corporations may be structured differently, Ms Leung indicated that:

"*I know in Johnson & Johnson they have a medical device business and a pharmaceutical business, and so they also have a centralised control structure where all their intellectual property is managed by the Patent Department or the IP group of J&J, the parent company. I know other pharmaceutical companies who have that structure....J&J is just one of them.*"

4.. The Celegne Transaction of 2019

134. Asked by counsel for BMS to describe briefly the Celegne transaction of 2019 and whether the acquisition approach was any different to the acquisition of the DuPont businesses, Ms Leung indicated that:

"*It was the exact same approach. Having worked on both transactions, I can say they were the exact same approach with respect to our centralised control structure and the creation of an acquisition sub...and* [that]*...the directors and officers of the acquisition sub that was successor to the Celgene sub were directors and officers and full-time employees of Bristol-Myers Squibb company.*"

5. The Scale of BMS

135. Asked by counsel for BMS about the scale of BMS between October 2001 and September 2002, Ms Leung indicated that during that time BMS had approximately 44,000 employees. Asked how many employees came across as a result of the acquisition of the DuPont businesses, Ms Leung indicated that approximately 2,000 employees came across.

6. The Task of Acquisition and Integration

136. Asked by counsel for BMS to describe the nature and scope of the task involved when entities

are acquired and integrated, Ms Leung indicated as follows:

> "*It is a massive effort, depending upon the size of the acquisition. And I recall that the DuPont acquisition, from the time I had at BMS, up until the time, that had been the largest one. It was* [a]*...close to $8 billion acquisition....*[I]*t involved – because when you do an acquisition, you have to develop certain synergies...you have to rationalise what employees stay, what employees go, what therapeutic areas in a pharmaceutical space...you'll continue to pursue, you have to decide benefits issues and integrate benefits plans. And so it is a massive effort. And we have a full team of employees full-time working on integration aspects. And the biggest issue I found in every integration is culture and getting the employees in both companies to work well together. Because one plus one should always, in an acquisition context, should always equal more than two. So, you have to build a better company, and that takes a lot of effort.*"

137. Asked by counsel for BMS how long this type of integration effort takes, Ms Leung indicated as follows:

> "*It's really facts and circumstance. I can say that with the Celgene integration, which has gone very, very smoothly – we took a lot of lessons in the past with integrations – that is still ongoing....*[W]*e closed that transaction in November of 2019* [and] [w]*e're almost done. I expect it'll take...another year or so to get everything done. It's a complex issue and so it's a very complex process. Some companies never fully integrate well. So, it's a multi-year effort.*" [In response to a later question, Ms Leung indicated that at the time of acquisition Celgene had approximately 8,800 employees and 10,000 patents.]

7. BMS Subsidiaries

138. Asked by counsel how many subsidiaries BMS Company had between September 2001 and October 2001, Ms Leung indicated that BMS Company had approximately 290 subsidiaries at that time. Counsel noted that Ms Leung had stated in her statement that:

> "*Decisions as to ownership of such acquired IP are, and at the relevant time were, made by BMS Co, and the Corporate Secretary group that I led in 2002 is and was involved in those decisions along with the IP department discussed above.*"

139. Counsel for BMS then asked Ms Leung to confirm whether, insofar as that engagement was concerned, it was managed from BMS Co or elsewhere. Ms Leung indicated that "*It was...managed by BMS Co, the parent company, and particularly our patent group.*"

140. Counsel for BMS noted that Ms Leung had indicated in her written statement that *"*[F]*ollowing the acquisition of DuPont Pharma by BMS Co, BMS Co made the decision to leave the IP assets held by DuPont Pharma with that entity.*" Noting that DuPont Pharma was re-named BMS Pharma, counsel for BMS asked whether this process was consistent with the corporate approach that Ms Leung had been describing to the court, Ms Leung indicated that it was "*entirely consistent*". Asked to confirm whether BMS Pharma had been a new entity or a name-changed entity, Ms Leung confirmed that it was the latter.

141. Asked later by counsel for BMS whether BMS Pharma had any employees after the acquisition was complete, Ms Leung indicated that it did not.

142. Asked later by me whether BMS Pharma had to observe procedural requirements, *e.g.*, if a board resolution was required or a shareholder resolution, Ms Leung responded:

"*No. It was a wholly-owned sub. And I know that I was an officer, or a director or officer of BMS Pharma. We never met. We understood that* [was] *our purpose and we were created for the sole purpose to benefit BMS Co.*"

8. Protection of Intellectual Property Rights

143. Counsel for BMS noted that Ms Leung had indicated in her written statement that the primary purpose behind the DuPont acquisition was to strengthen BMS's "*virology and cardiovascular franchises*". He then asked her to expand about the need in this context to have control of intellectual property rights. Responding to this invitation, Ms Leung indicated as follows:

"[T]*his was a new business for us in many ways....IP litigation is inevitable for innovator companies....*[S]*o it was important that we be able to control, make decisions in the best interests of BMS Co with respect to IP litigation and protecting our IP rights....*[T]*he way we operated....*[a]*ll decisions related to IP, protecting our IP, promoting our IP and protecting it, were made by BMS Co and particularly the IP lawyers employed by BMS Co. So, all decision-making...was centralised, unfettered and complete.*"

9. The Email of 29th October 2001

144. Turning next to the email of 29th October 2001, counsel for BMS noted that (i) Ms Leung in her written statement (a) speaks about the recommendation in that e-mail being "*in accordance with the decision-making and general policy and practice of BMS Co described above whereby acquired IP is often left in the acquired wholly-owned subsidiary*", (b) notes specifically that "*legal ownership of BMS Pharma's IP assets remained with DuPont Pharmaceuticals Company, and the name of that entity was later changed to the new name, Bristol-Myers Squibb Pharma Company*", and (ii) she also refers in her written statement to the ability of BMS Co to decide at any particular time what to do with that IP, including placing it wherever it wished. He then asked Ms Leung (on my reading) to expand on point (ii), at which point Ms Leung indicated as follows:

"*Well, decisions had to be made in respect of IP, depending upon what's happening at that time, if our IP is challenged. And so it's important that we have...centralised control over decisions as to what filings to make in court, things of that nature. So, it was really important that the BMS IP department – again, the employees, they were full-time employees of BMS Co – make those decisions. And that was so, even though the IP was held in BMS Pharma Company, it was clear that BMS Pharma Company was created to act, or the beneficiary of that was BMS Co.*"

C. Cross-Examination

1. Error in Making of 652 Application

145. Counsel for Teva began by noting that Mr Golian had acknowledged that the application for 652 should have been made by BMS Pharma. The following exchange then occurred between counsel and Ms Leung:

Counsel:	...[H]*ave you discovered since how that mistake came about?*
Ms Leung:	*I don't know how it happened. I'm disturbed to learn that it happened. It was clearly a mistake and it was contrary to the directions of the policy of the company.*
Counsel:	*....When did you learn of that mistake?*
Ms Leung:	*I believe it was in the context of this litigation or before. I don't recall precisely...but it was...many years...decades...after it happened.*

Counsel: ...[W]*as it only at the time of this litigation..?*

Ms Leung: *I don't recall if it was specifically in the context of this litigation. But...it was definitely in the context of the Eliquis patent litigation....*

Counsel: [W]*hen you learned of the mistake, did you carry out an investigation to ascertain how the mistake occurred?*

Ms Leung: *No. It happened decades ago....*

Counsel: ...[M]*any of the people that were involved in it at the time...are still employees of BMS, isn't that correct?*

Ms Leung: *Yeah....*

Counsel: *So, even though it happened decades ago, you could've made enquiries of them..?*

Ms Leung: *...I could have....Would it have been wise to do it is another question? ...*[I]*n my view, something that happened decades ago that was a clearly a mistake...I didn't feel it was the best use of my time to carry out an investigation into a mistake that happened decades ago....*

Counsel: ...[Y]*ou knew that one of the issues was how this application had been made in the name of BMS..?*

Ms Leung: *Yes....*

Counsel: *And even at that stage you didn't...ask any of the people involved...how this mistake was made?*

Ms Leung *....I didn't think it was the best use of my time...for an error that happened decades ago that...I wish...hadn't happened...but...did....I didn't feel it was the best use of my time to investigate...that.*

Counsel: *None of the experts...have said* [that] *this was a mistake.*

Ms Leung: *I don't know what the other experts have said.*

Counsel: ...[B]*ut the experts on behalf of BMS. I'm sure you're aware...what they're saying..?*

Ms Leung: *What I'm aware of is that the policy of BMS was not followed in this particular instance. And I understood from Mr. Golian's testimony yesterday that mistakes similar to this were made...and there were three attorneys who made the mistakes. And unfortunately, I have found over years that sometimes people get instructions and...still don't follow them. It's...frustrating....And it was...as simple as that...a mistake that should not have happened.*

Counsel: *The first this court learned that BMS acknowledged it was a mistake was yesterday.*

Ms Leung: *I don't know when the court knew* [the] *information, so I can't confirm that was the first time....*

Counsel: *When preparing your statement...you didn't tell the court that a mistake had been made? ...*

Ms Leung: *I didn't think it was relevant to my statement....because it didn't detract from the fact that it was the policy of BMS Company that when we acquired a company that our IP department would have centralised, unfettered and complete control over the IP and that instructions were given, because we strive for consistency, and unfortunately sometimes that consistency is not achieved. And unfortunately, I've learned over the years that that's what happens sometimes. And so, I didn't think it was relevant in that sense, because it didn't detract from the main point that our policy was to have...complete control over the IP of...acquired companies....*

Counsel: ...[W]*hat...firms of lawyers are handling this litigation? What US firms, firstly?*

Ms Leung: ....[T]*he primary US firm is WilmerHale.*

Counsel: *Were they told that this was a mistake?*

Ms Leung: *I don't know....*

Counsel: *Was Judge Holland told this was a mistake..?*

Ms Leung: *I don't know....I don't recall reading in...*[Judge Holland's] *statement that he was told it was a mistake....*[T]*hat didn't surprise me, because it was simply...a mistake. It shouldn't have happened. It did. And...it didn't detract from the main point of what the company's policy was.*

Counsel: ...[D]*id you think the expert opining on this issue for the court should've been told that a mistake was made by BMS?*

Ms Leung: *...I...trust...my IP team and our outside counsel...would have provided the expert with...all and any necessary information....*

Counsel: *Am I correct that the policy was that this application should've been made by BMS Pharma?*

Ms Leung: *I understand there was an instruction that was given....I guess you can call it a policy...that it should've been filed in the name of BMS Pharma, but it was not.*

Counsel: ...[A]*re you aware that Judge O'Moore, in this jurisdiction, was told a year ago that BMS's policy was implemented in respect of this patent?*

Ms Leung: *I'm not aware of that.*

2. The Emails of October 2001

a. The Email of 19th October 2001
(The Robert Souka Email)
[The text of this email is set out in chapter 2]

146. Counsel for Teva brought Ms Leung to the email of Mr Souka of 19th October 2001, drew her attention to the reference therein that BMS Pharma *"houses most of the intangibles*" and suggested that "*those were most of the intangibles acquired in this acquisition*". To this Ms Leung responded that the email was sent by Mr Souka and that "*I don't know what he knew. And as I sit here now, I don't know if 'most of the intangibles' is a correct statement....I've no reason to doubt it, but that's what's in Bob Souka's e-mail.*"

b. The Email of 24th October 2001
(The Francis Rossi Email)
[The text of this email is set out in chapter 2]

147. Counsel for Teva brought Ms Leung to the email of Mr Rossi of 24th October 2001 and to the reference therein to maintaining in BMS Pharma the legal ownership of patents and trademarks related to the pharmaceutical business, with new patents and trademarks to be in the name of BMS Company. The following exchange then ensued between counsel for Teva and Ms Leung:

Counsel: [W]*hat do you understand by the reference to new patents and trademarks?*

Ms Leung: *Any new patents or trademarks...filed after the date of the acquisition.*

Counsel: *So, if there's a filing for US 652 after the acquisition, is this suggesting that it should be in the name of BMS?*

Ms Leung: *I understand there was a subsequent e-mail that related to...earlier patents that were filed in the context of priority, that it should be in the name of BMS Pharma....*

Counsel: *But what did you understand by the statement as written here?*

Ms Leung: *I think the statement doesn't deal with the issue of priority....*
Counsel: ...[T]*his e-mail doesn't deal with the priority issue at all in respect of...a patent where a provisional application had been made prior to 1st October 2001?*
Ms Leung: *That's what I believe. Because Margaret Yonco-Haines is a tax lawyer and not a patent lawyer...and I know Margaret...and I've never talked to her about priority or patent-related issues in this context. So, I would be surprised if she was referring to prior patents.*

148. Later in his cross-examination, counsel returned to this email and noted that lower down in the email chain, in an email sent by Margaret Yonco-Haines (in truth, the principal email in the chain), Ms Yonco-Haines writes:

> "*We have determined the following three categories of 'Du Pont Pharma' patents and trademarks, based on the business to which the intangibles relate. Please let us know if any of our recommendations for legal entity registration of these intangibles doesn't make sense from your perspective...*".

149. Counsel for Teva focused in on the word "*recommendations*", the following exchange occurring between him and Ms Leung:

Counsel: *That's what the e-mail says, a recommendation.*
Ms Leung: *You can call it a recommendation, but my understanding, based on my knowledge, is that that was the longstanding consistent policy of BMS Co.*
Counsel: *But isn't it strange that the writer of the e-mail put it forward as a recommendation, if in fact that was the longstanding policy? ....*
Ms Leung: *I don't read much into the use of the word 'recommendation' or 'policy'....All I know...as I read the e-mail now and as I read it then, it was not unusual, it was the consistent policy of the company.*
Counsel: *But...she says: 'Please let us know if any of our recommendations for legal entity registration of these intangibles doesn't make sense from your perspective.' Doesn't make sense....*
Ms Leung: *I believe she wrote that because there could be instances where it makes good business sense to treat it differently....*
Counsel: *I have to suggest to you, Ms. Leung, that that is inconsistent with a longstanding policy that was known to everybody, that was invariably applied, as you have suggested?*
Ms Leung: *....I disagree with you on that....I think it's entirely consistent because there are always situations where there are good business reasons to differ from the policy or take a different position....*
Counsel: *So...there may have been other cases where this policy wasn't followed..?*
Ms Leung: *If there were good, solid business reasons as the parent company...we would make a business decision on how to treat those assets in the exercise of our central, complete and unfettered control of the assets of the acquired company.*
Counsel: *So, in respect of different situations, a decision would be made as to where to house the patents..?*
Ms Leung: *It depends on the facts and circumstances....*
Counsel: *....So, it wasn't an invariable policy, it was...a question of making a business decision, depending on the facts..?*
Ms Leung: *No...*[T]*hat was the policy of the company, but if there were good*

business reasons to make a different decision in the exercise of our central, complete and unfettered control of the assets of the acquired company...we could have made a different decision. In this case, with the DuPont acquisition...the policy was implemented as it normally is.

3. The Email of 30th January 2002
(The Blair Ferguson Email)
[The text of this email is set out in chapter 2]

150. Asked when she first encountered Mr Ferguson's email, Ms Leung indicated that she did not recall specifically when it was shared with her. "*It was probably sometime in the summer or fall of last year.*" Asked if the email struck her as important when she saw it, Ms Leung indicated that when she saw it and understood it in the context of the litigation, it was clear to her it was important. However, she noted that "*it was also consistent with our policy....*[s]*o, it wasn't striking in that sense. But I do recall that it was an e-mail that I reviewed and I've noted that it was consistent with our longstanding policy.*" Asked if she thought that she should have referred to it in her statement, Ms Leung indicated that:

> "[A]*s I sit here now, I still take the view that it wasn't relevant to my statement. Because again, it didn't detract from the company's longstanding policy that...BMS Co controls the IP of acquired companies centrally and completely through our IP department. So, it doesn't detract from that at all. And in my view that was a principal point of my statement.*"

4. Previous Advice on Policy

151. Counsel for Teva turned next to whether Teva had previously obtained an opinion analysing equitable ownership as a basis for claiming priority. At this point the following exchange occurred between counsel and Ms Leung:

Counsel:	*Mr. Golian, yesterday, said you never got any opinion at any stage confirming that...the priority right was enjoyed beneficially by BMS....*[that] *no legal opinion was ever obtained containing an analysis of equitable ownership as a basis for claiming priority?*
Ms Leung:	*...I don't know for a fact if any opinion's been obtained....I know that we did consult with some Delaware law experts on this issue of beneficial ownership, and I did have an opportunity to read their opinion.*
Counsel:	*But that was in connection with the litigation when this issue was raised. That was the first time, isn't that correct?*
Ms Leung:	*I don't recall. I don't know.*
Counsel:	*Well, you have not seen any such opinion....analysing equitable ownership as a basis for claiming priority, apart from the opinions offered by the experts in this litigation?*
Ms Leung:	*I don't recall seeing any such opinion. And I don't think that would be unusual, because I also know how we acted. And we acted as beneficial owners.*

5. The Email of 12th June 2002
(The Dora Lynch/Manual Email)

152. Turning to the substance of the email of 12th June 2002 (the text of which is set out in chapter 2) and the status of in-house BMS Manual, the following exchange occurred between Ms Leung and counsel for Teva:

Ms Leung: *I'm referring to an e-mail that's to a large group of people from Dora Lynch dated June 12th, 2002. And the subject is 'Administrative Training Manual'....*

Counsel: *And I think you were here yesterday, I'm not going to delay, the people who were recipients of that e-mail were identified?*

Ms Leung: *Yes, I think they were members of the patent group.*

Counsel: *Exactly. And it contained both lawyers and paralegals, isn't that correct?*

Ms Leung: *That's correct.*

Counsel: *And Blair Ferguson, at the time, was the chief patent counsel....*

Ms Leung: *I don't believe his title was Chief Patent Counsel. That may have been the title he had at DuPont...but he was not...the head of the patent group at Bristol-Myers Squibb Company....*

Counsel: ...[D]*o you want to say to the court whether you regard this as a guidance or an instruction or an expression of policy?*

Ms Leung: ...[T]*his is a handbook...*[I]*t was an effort to achieve consistency within our patent group, which was a fairly large group, with a lot of administrative-type work. So, it was an effort to establish some, whether you call it policies or guidelines. The intent was to ensure some consistency among the group.*

Counsel: ...[I]*t was instructing both the lawyer recipients and...paralegals as to the procedure to be adopted..?*

Ms Leung: *Instructing? I think it was laying out a desired uniformity that everyone should follow....*

Counsel: ...[T]*he expectation was that it would be followed..?*

Ms Leung: *It was the expectation and goal, I think, of this handbook....It was issued by a paralegal in the team.*

Counsel: *Yes, but it was approved by the lawyers..?*

Ms Leung: *I don't know for a fact whether it was approved by lawyers and I don't know if a lawyer said 'Okay, that makes sense' or...'I endorse it and everyone one should follow it'....I just don't know....*[The] *handbook was not shared with me outside the context of this litigation....*

Judge: [I]*f Blair Ferguson was copied on it, would that not suggest it came with his imprimatur..?*

Ms Leung: *That's correct. I don't know who endorsed it, what patent lawyers, if any, endorsed this handbook.*

Counsel: *And you have never come across any response saying this is not acceptable, this is incorrect, this is a misunderstanding, this doesn't represent the policy of BMS, isn't that correct?*

Ms Leung: *No, nor would I expect to be.*

Counsel: ...[I]*f it was wrong and not being adopted, you would expect such a response..?*

Ms Leung: *I don't know if it would come to my attention...as General Counsel.*

Counsel: *....Well...you would expect that such a response would've issued, even if it hadn't come to your attention at the time?*

Ms Leung: *There have been occasions – and I'm just putting my answer in context – where something may be issued and...some employees may not agree with something, but they don't say anything and they just don't follow it. And that's just the reality of the workplace sometimes.*

Counsel: *Well, as the judge put it to you, if Mr. Ferguson and some of the*

other senior lawyers [copied]*...thought this was incorrect, you would have expected them to have so responded?*

Ms Leung: *I would hope that they would've done that....*[b]*ut my experience is that doesn't always happen.*

Counsel: [And]*...it's made clear that...*['The] *collective attorney group can agree to make changes, but no individual attorney can make procedural changes.'* You're aware of that? ...

Ms Leung: *Yes. Yes, I see that....*

[b. Chapter 13 of the Manual]

Counsel: *And you're aware that while any manual...might evolve, that Chapter 13, dealing with the issue with which the Court is concerned, remained essentially the same up until at least 2005..? ....You were aware, I take it, of Chapter 13, which is the chapter that has generated the controversy in this...*[litigation]*?*

Ms Leung: *I'm aware of Chapter 13 relating to provisional applications....*

Counsel: ...[W]*hen did you become aware of that?*

Ms Leung: *I don't know the precise date. But again, it was in...preparing for this litigation.*

Counsel: *And you will have seen...the paragraph at the top of the page....*

[This is the paragraph in Chapter 13 that states as follows, under the heading "*Assignments for non-provisional cases*":

> "*All DuPont Pharmaceutical Company (DPC) cases which claim priority to a filing date prior to 10/1/01 should be in the name of...BMS Pharma....Thus, if the provisional is filed prior to 10/1/01, all subsequent filings worldwide claiming this priority should be in the name of BMS Pharma. BMS Pharma is a Delaware general partnership. For all Wilmington cases having an earliest priority date after 10/1/01, the name of assignee should be...BMS....You will need to change the Recordation Cover Sheet to enter* [BMS Pharma]*...as the form defaults to* [BMS Company]."]

[W]*hat was the purpose of this instruction that the application should be made in the name of BMS Pharma?*

Ms Leung: *This was implementation of the company's longstanding policy with respect to ...handling...IP of an acquired company.*

Counsel: ...[T]*he purpose of it, Ms. Leung...was to obtain priority in respect of the application..?*

Ms Leung: *I think the purpose of this instruction to paralegals in the patent group was to obtain uniformity in how we handle this in implementing our policies....*

Counsel: *But the purpose of that uniformity was to obtain priority..?*

Ms Leung: *Yes, I think that makes sense, that the purpose was to maintain priority....*

[c. Non-Compliance with Manual and Impact on Priority]

Counsel: *And it was understood by BMS that...to obtain that priority, the application had to be made by BMS Pharma..?*

Ms Leung: *I don't agree with that....*[I]*n the event that it wasn't made in* [*sic*

– by?] *BMS Pharma...I don't think it's fatal to our application...because we were beneficial owners of...the IP assets of DuPont Pharma.*

Counsel: *So you say. When was the first time you thought and considered, Ms. Leung, that this was not fatal to the priority that you've claimed, the fact that you hadn't followed this policy?*

Ms Leung: *As...I was preparing for my testimony in this case and...came to understand the facts and the events in this case....*

Counsel: [T]*hat was in August...*[2022]?

Ms Leung: *...I don't recall precisely when I first learned of the issue or when discussions were made....*

Counsel: *You deal in...*[your] *witness statement with beneficial ownership.*

Ms Leung: *With respect to our longstanding policy of complete control, yes.*

Counsel: *And you knew, at that stage, that you were addressing this issue of priority...? ....And therefore, we may take it that you spoke to...people...in general terms on this issue at that time?*

Ms Leung: *Yes, I spoke to them about the facts and how we actually acted at the time of the acquisition and a longstanding policy....*

Counsel: *And you would know from your own knowledge that the priority issue is a crucial issue..?*

Ms Leung: *Yes.*

Counsel: *And you would know from your own knowledge that the identity of the entity that applies for a patent is critical in terms of preserving priority?*

Ms Leung: *I believe so....*

Counsel: *And you say you spoke to outside counsel..?*

Ms Leung: *Yes.*

Counsel: *And is that WilmerHale?*

Ms Leung: *I don't know if any WilmerHale lawyers were on the call. I don't recall, as I sit here now, who exactly was on the first call or any calls in general.*

...

[d. Chapters for Lawyers]

[After counsel for Teva noted that Chapter 17 is headed "*Notices of Appeal*", chapter 18 is headed "*Appeal Briefs*", and chapter 21 is headed "*Decisions of the Board of Patent Appeals and Interferences*", the following exchange occurred between counsel and Ms Leung:]

Counsel: *All of those chapters are relevant to the lawyer..?*

Ms Leung: *I have no doubt that the lawyers are aware and didn't use that….*[A]*gain, this is the handbook for paralegals, yes.*

Counsel: ...[I]*t's also directed in these chapters at least to the lawyers..?*

Ms Leung: *I believe so....*

Counsel: [T]*herefore, the lawyers would be familiar with this document which you very much hoped would be followed and obeyed..?*

Ms Leung: *It would be my expectation but, again, human experience tells me not everyone follows what you expect them to follow....In a large company like BMS there are many handbooks, procedural documents and not everyone reviews everything that you expect them to....*

Counsel: [The manual] *was directed to the paralegals and lawyers in the Patent Department, handling patent applications and patent briefs, isn't that correct?*

Ms Leung: *That's my understanding in reading the document.*

Counsel: *And I fully accept that you might be disappointed from time to time somebody might not follow it? ....But being aware of its existence is something you would expect of all of these paralegals and...lawyers?*

Ms Leung: *I would hope so, but, again, I don't have the full context for this handbook.*

[e. Compliance, Conformity, and Corporate Governance]

Counsel: *You were in charge of compliance at this stage..?*

Ms Leung: *I had responsibility, in 2002, as office of corporate conduct which was the predecessor to our official compliance and ethics group....*

Counsel: *And...compliance means ensuring that people follow the rules or...instructions or...guidance..?*

Ms Leung: *In a large company of 44,000 people in a highly-regulated industry, there are many rules and regulations we must comply with....There are many...handbooks and procedural documents at BMS and it would not be the responsibility of the compliance group to make sure that every employee complied with every requirement in every handbook.*

Counsel: *...BMS boasts about its corporate governance, isn't that correct? ...*

Ms Leung: [W]*e're proud of our corporate governance....*

Counsel: *And part of corporate governance is ensuring compliance with rules and instructions, some of which will inevitably be more important than the others. But it's part of that culture of compliance and corporate governance of which BMS speaks..?*

Ms Leung: ...[I]*t's acting with integrity and acting and...*[having] *a compliance culture where we comply with policies and procedures....But this is a procedural document....*

Counsel: [P]*rocedures in relation to ensuring priority of patents are essential, isn't that correct?*

Ms Leung: *I agree that it is important....*

Counsel: [T]*herefore the importance of the senior lawyers and others complying with this is obvious?*

Ms Leung: *I 'on't know what you mean by 'obvious' in this context....*

Counsel: *It was clearly important to BMS that lawyers and paralegals would comply with these procedures on priority?*

Ms Leung: ...[A]*gain...this was an effort to achieve uniformity. I don't believe...compliance with every single item was important....I don't have that context to say if you 'on't follow this handbook it would be fatal to our applications.*

Counsel: ...[Y]*ou were aware that my question said it was important to comply with the procedures for priority....*

Ms Leung: *I think it's important to comply with procedures for priority....And that filings are made appropriately....*[But] *I can't tell you that this handbook and failure to comply with every aspect of this handbook would put us out of compliance....*

Counsel: *I didn't ask about putting you out of compliance, which is a different issue....You would expect senior lawyers and paralegals to comply with the procedures relating to priority?*

Ms Leung: *...I believe it is important to comply with procedure designed to protect our priority rights. I agree with that. I don't know if that is centrally connected to this handbook that was issued in 2002.*

Counsel: *...And you would expect the senior lawyers and...paralegals to understand the importance as well?*

Ms Leung: *The importance of following and ensuring that our filings related to priority and other IP filings were done correctly and appropriately; I agree that is important. I don't agree that the only path was if you followed everything in this handbook.*

Counsel: *And you would understand that anybody who was working in the Patent Department...would have had an obligation, at least, to the company to be familiar with this rule book and, in particular, the rule book in relation to priority applications?*

Ms Leung: *...I can't say that because even looking at the introduction of the handbook it says:'I'll be shocked if the manual doesn't contain errors, redundancies and the like, and if it isn't too detailed in some places and not detailed enough in others.'* ...[That] *doesn't inspire confidence in me that this was the only path to have proper filings to protect priority and other IP issues....*

Counsel: *They would have had an obligation to be familiar with it, Ms. Leung?*

Ms Leung: *I don't know if that is the case....I would hope that they read it.*

Counsel: *Would you expect them to read it, having regard to their duty to the company?*

Ms Leung: ....[T]*his is not...*[a] *document that requires certification that you've reviewed it and I didn't view it in the same category of the group of documents that I would expect every single employee at BMS to review and certify that they've certified, understood, and will comply with.*

[f. Draft or Work in Progress?]

Counsel: *You described it as a draft but I've already pointed out to you that at least up until 2005, Chapter 13, dealing with priority, remained essentially the same?*

Ms Leung: [It itself states that] '*This is very much a work in progress.'*

Counsel: ....[Y]*ou now have the additional information that it remained in this state up to 2005; do you still think it's appropriate to call it a draft?*

Ms Leung: *....My experience again tells me there are drafts that live for years....*[a]*nd some drafts are never finalised.*

Counsel: *Well, you know the difference also between a work in progress and a draft, don't you? ....It might be something that people are working on, expected to follow in its present state, but acknowledging that other ideas may be passed on and provided that would suggest improvements could be made.*

Ms Leung: *Again, to me work in progress means it's not final....*

Counsel: ....[Y]*ou would expect most training manuals to be work in progress, wouldn't you? ...*

Ms Leung: *....I've seen training manuals both in draft and finalised.*

6. Other Available Witnesses

153. Counsel for Teva noted that some persons who remain in BMS and were involved in the BMS Pharma acquisition have not been called to testify in these proceedings. Ms Leung expressed a supposition that anyone who had relevant evidence had been asked to testify, though she acknowledged that this decision (as to who should testify) was "*made by our counsel who are most familiar with the facts*".

7. Reliance on Beneficial Interest

154. Counsel mentioned that a witness statement by Ms Marla Mathias, an ex-employee of BMS, had been relied upon in Sweden but is not in evidence in the present proceedings. This, and the question of when and how BMS came to rely on a beneficial interest formed the subject of the below-quoted exchange between counsel for Teva and Ms Leung. The following exchange occurred in this regard:

Counsel:	[Y]*ou'll have noticed* [that] *in her statement she* [Ms Mathias] *makes no mention of beneficial interest..? ...*
Ms Leung:	*I don't see any reference to beneficial ownership, nor do I find that unusual....*
Counsel:	*Even though she was addressing the priority issue?*
Ms Leung:	*But it's clear...that she...understood, that the e-mails were...stating our...longstanding policy....*
Counsel:	*So, the e-mails state your longstanding policy. And those e-mails are 'Maintain legal ownership in BMS Pharma' ....*
Ms Leung:	*I believe that's...what it said.*
Counsel:	*And she said it was a no-brainer to leave the patents where they were because they could be called for at any time..?*
Ms Leung:	*I do recall the reference to no-brainer....*
Counsel:	*So, obviously you had access to them because you could call for an assignment at any stage..?*
Ms Leung:	*Yes, because, again, BMS Pharma was a wholly-owned subsidiary for BMS Co.*
Counsel:	*....And what she envisages in her statement is, the fact that it was a wholly-owned subsidiary would entitle BMS to call for their assignment at any stage?*
Ms Leung:	*I don't know what she put that basis on but I know that all the actions of BMS Pharma were done for the benefit of BMS Co.*
Counsel:	*When you say all of the actions were done for the benefit of BMS Co, I take it you're referring to the fact that under Delaware law, where a subsidiary acts, it must act in the best interests of the holding parent..?*
Ms Leung:	*I'm not just referring to Delaware law, certainly the structure supports that. But the way we in fact acted and fact that BMS Pharma did not have meetings, did not have employees and it was created and existed for the purposes of ensuring the best interest of BMS Co.*

8. Corporate Structure in and post-2001

155. Counsel engaged in a series of questions that elicited the following information from Ms Leung:

(i) BMS Pharma existed as a legal entity after the acquisition;

(ii) it took over all the assets that were in DuPont and it continued to exist because there were some contracts and other things that were still in the name of BMS Pharma.

(iii) it continued to house the patents but all the directors and officers of BMS Pharma were employees of BMS Co and they understood that in their role as directors and officers of BMS Pharma "*that they operated, and the reason why BMS Pharma was created, was to serve the...best interest of...BMS Co.*"

(iv) what transpired was not just a name change. "*There was a complete change*

of directors and officers and the directors and officers were employees of Bristol-Myers Squibb Company. It...[was] *not a mere name change....It was a completely different purpose of BMS Pharma versus the former DuPont entity...acquired by BMS.*"

(v) prior to the acquisition it is a "*fair assumption*" that its directors were employees of the parent company of DuPont Pharma.

(vi) such arrangements are "*frequently done as corporate structures....*[T]*hat was our structure and the structure of J&J and other companies...I'm familiar with*".

(vii) when it was put to her that "*It's not unusual, in the...pharmaceutical sector, to have other companies or...groups structured in the same way where you have subsidiaries in which patents are housed or owned and you have directors being employees of other corporate companies or of the parent company*", Ms Leung indicated that she would think having employees of the parent company as such directors: "[A]*t BMS, the parent company employees became directors and officers of wholly-owned subsidiaries*".

(viii) it would not be unusual, in such structures, to have the patent lawyer section or legal section centralised in the parent company. "[A]*t BMS...patents are controlled by one patent department.*"

9. Email exchange of 26th March 2002
(The Ferguson/Carini Emails)
[The text of these emails is set out in Chapter 2]

156. Counsel drew Ms Leung's attention to an email likely sent in March 2002 from David Carini email in which Mr Carini writes:

"*Blair, I had to have assignment papers for a CDK patent redone in the name of BMS Pharma after they were initially done in the name of BMS. I assume that this was done because the initial invention and/or filing was done in DPC. Is it the invention or the provisional filing that must have occurred when we were still DPC to make it a BMS Pharma case.*"

157. Mr Ferguson responded to this email inquiry on 26th March 2002 in the following terms:

"*All cases having a provisional filing date on or after 10/1/01 will be assigned to BMS. All cases having a provisional filing date before 10/1/01 should be assigned to BMS Pharma.*"

158. After bringing Ms Leung to these emails, the following exchange transpired between counsel for Teva and Ms Leung:

Counsel:	*That's what Blair Ferguson was telling David Carini?*
Ms Leung:	*Yes....*
Counsel:	*And that would not have been necessary if BMS had the equitable title to the patent and the priority rights associated with it..?*
Ms Leung:	*I don't necessarily agree with that. I think BMS did...have...beneficial ownership of the IP that we acquired in DuPont.*
Counsel:	*But that would not have been necessary if it in fact had it..?*
Ms Leung:	*I don't know what you mean by necessary or not. I mean...this was the consistent policy of BMS Co.*
Counsel:	*And the reason it was the consistent policy, I suggest to you, was that it was recognised that you couldn't, and didn't have, beneficial title in these acquired patents.*

Ms Leung: *I don't agree with that at all.*

10. Judge Holland, Searching for an Assignment, and Beneficial Interest

159. Judge Holland notes in his statement that extensive search had been made within BMS for a written assignment in the 2001-2002 timeframe from BMS Pharma Company to BMS of the right to claim priority from the first patent filing. This led to the following exchange between counsel for Teva and Ms Leung:

Counsel: [W]*hy would an extensive search be made for an assignment that everybody knew, by reason of the policy of the company, wouldn't have existed?*
Ms Leung: *I don't know what was meant by the extensive search.*
Counsel: *Very odd, isn't it?*
Ms Leung: *No, I don't find it odd....*[a]*nd the reason I don't find it odd...*[is] *because I know that has been the longstanding policy of BMS....*
Counsel: *But why would people make an extensive search if everybody knew you didn't have assignments, because you relied on the policy?*
Ms Leung: *I don't know what an extensive search means...I don't know who they spoke to. So, I can't tell you. And I don't find it peculiar at all....The point here is that I know this is the policy of the company. Whether it was written, I've never seen a written policy, nor do I think it's necessary to have a physical piece of paper saying this is the policy, because that is the way we've always conducted our acquisition of companies, handled the assets of acquisitions of companies in my nearly 31 years at the company.*
Counsel: *An extensive search for an assignment, that's what he says....*
Ms Leung: *I certainly think that a good faith and diligent effort was made to look for the assignments. I don't know the details....*
Counsel: *And when an assignment wasn't found, they then went to Justice Holland to say is there another basis for claiming priority?*
Ms Leung: *I don't know that happened....*
Counsel: *...I suggest that the first time BMS sought to rely on a concept of beneficial ownership to protect the priority was after it was discovered there was no assignment.*
Ms Leung: *I would say we were relying on the facts of what actually happened here.*

160. It does not take a great deal of inspiration to deduce that the reason BMS likely looked for the assignments is because it would make its life easier if they existed. In his closing submissions (which I accept are not evidence), counsel for BMS adverted to this rationale, observing "[T]*here's been lots of straw men in this case; it was said why is Justice Holland referring in his report to a search for an assignment? It's obvious. If an assignment existed, then they didn't have to worry about it.*"

11. Right to Call for Assignment of Asset

161. Counsel for Teva turned next to the power of a parent company, under Delaware law, to call on any subsidiary to assign any asset of that subsidiary to it, and the consequences of that power.

Counsel: ...[A]*m I correct in saying under Delaware law that a wholly-owned parent can call on any subsidiary to assign any asset to it?*
Ms Leung: *Any wholly-owned subsidiary, yes.*
Counsel: *So, the fact that BMS had a right to call for the assignment of the*

asset...wouldn't differentiate BMS from any other parent with a wholly-owned subsidiary?

Ms Leung: *No...*

Counsel: ...[O]*ne thing we do know is that notwithstanding that unfettered right, as described, to call for the asset, the parent company doesn't normally have a beneficial interest in the assets of the subsidiary. We know that? ...*

Ms Leung: *I know that in this case BMS Pharma was a wholly-owned subsidiary of the parent company, BMS Co, and we...had the ability to control the IP, and we did in fact do that.*

Counsel: *...The fact, or the right that a parent may call for an asset to be assigned to it by its wholly-owned subsidiary does not in itself create a beneficial interest in that asset, is that correct?*

Ms Leung: *I'm not an expert in Delaware law....I can tell you what I know about in this case is that we exercise complete control of the IP...all aspects of BMS Pharma....*

Counsel: ...[Y]*ou cannot tell this Court whether you, of your own knowledge, know if it's a principle of Delaware law that the right of a parent to call for an asset from the wholly-owned subsidiary does not in itself create a beneficial interest? You don't know whether that principle is correctly stated by me or not?*

Ms Leung: *I can tell you that I am not an expert in Delaware law and I would defer to the experts in Delaware law....I don't want to opine on an area where I don't know for sure and I'd leave it to the Delaware law experts....*

Counsel: *So, there's no misunderstanding, you don't know whether the principle so stated by me is correct or incorrect?*

Ms Leung: *That's correct....*

12. Absence of Advice Concerning BMS Practice

162. Counsel for Teva turned next to the related issue of whether BMS had ever sought advice concerning its general practice of leaving acquisition assets in a subsidiary.

Counsel: *So, for 16 years, you have presided over acquisitions with a policy you state of leaving the assets in a subsidiary on the basis that BMS has a beneficial title to those, but you don't know what are the relevant principles of Delaware law, is that the position?*

Ms Leung: *I'm not saying that at all. All I can tell you is that I am not an expert in Delaware law and I'm hesitant to provide an opinion on a point of Delaware law. I can tell you what the facts were in this particular case and how BMS acted....*

Counsel: *And yet you say in your statement that under Delaware law, BMS owns a beneficial interest in the assets of BMS Pharma?*

Ms Leung: *Yes.*

Counsel: ...[W]*hat is the basis for that statement..?*

Ms Leung: *My general knowledge...I understand the concept overall of beneficial ownership....*[W]*e were the owners of the IP assets and all the assets of the acquired entity, or the acquired assets from DuPont....*

Counsel: *And you have already told us you never saw an opinion prior to the Holland opinion stating that the view of a legal expert in Delaware law was that BMS had a beneficial interest in the patents of its subsidiaries, you never saw such an opinion? ...So...BMS, a company with...an annual turnover of hundreds of billions, has all*

of these valuable assets in a subsidiary on foot of a policy that is nowhere recorded and that is premised on a belief that you, as Head Counsel, can't confirm from your own knowledge or expertise that it enjoys a beneficial interest in those patents; that's your evidence..? ...

Ms Leung: *...I can tell you again the facts here as I know it and understand it is that this was the longstanding policy of BMS to hold the assets of an acquired company into a wholly-owned subsidiary....And we have exercised complete control over the assets.*

Counsel: ...[T]*hese assets are the core of BMS, isn't that correct, the most valuable assets? ...IP assets?*

Ms Leung: *IP is certainly a critical asset of an innovative pharmaceutical company....*

Counsel: *And you say from back then till now, when you take over, including the Celgene, the IP is left in the subsidiaries..? ....And you personally don't know, from your own expertise, whether that gives BMS a beneficial interest in those IP assets?*

Ms Leung: *I believe that it does, because I understand the concept of beneficial ownership. We act as owner of the asset and we are in fact the owner of the asset, and that's how we've acted and controlled the assets of the....acquired company....*

Counsel: ...[A]*nd you never got any legal opinion to that effect, you yourself are not in a position to make that assessment, is that correct?*

Ms Leung: *I have not asked for a legal opinion on beneficial ownership of these assets. Nor did I feel it was necessary to do so. Because again, over the extensive period of time I've been at BMS, this is how we acted and there's never been, at least I've* [never]*been involved in a situation where there was a question about whether or not we had beneficial ownership of these assets....*

Counsel: ...[W]*hat do you think the Board would say if it was told by its Head Counsel defending all of this litigation that actually, we preserve our rights in these valuable patents on the basis of a belief that we have a beneficial interest, but we never received an opinion to that effect and nobody seemed to operate on that basis? What do you think the Board would say?*

Ms Leung: *I don't think the Board would think anything of it, because they know that's how we've acted....over many...years. And so it would seem odd to me to seek a legal opinion on what*['s]*...been the longstanding policy of BMS....and has not been an issue....*

Counsel: ...[C]*ould you tell us what document exists that the Board has seen which explains to the Board that there is a beneficial interest in the patent assets held by wholly-owned subsidiaries of BMS, what document tells them that's the policy?*

Ms Leung: *I can't point to a specific document, but I could tell you that when we review with the Board, in the context of an acquisition, how we plan to handle it and all matters related to integration, they certainly have visibility on how we handle the assets of the acquired company and they understand that...on day one of integration...there is a wholly-owned subsidiary where the assets of the acquired company may go into and...it's a wholly-owned subsidiary in complete control and decision-making is made by employees of BMS Co.*

Counsel: ...[I]*f the Board hasn't seen any such document, does any such document exist anywhere in BMS or any of its subsidiaries?*

Ms Leung: *I am not aware...of a document that says that we are the beneficial*

owners of assets...of an acquired company that we put in a wholly-owned subsidiary of BMS, nor do I think it's necessary....

Counsel: *So there is no written document supporting the proposition that BMS has relied on in this litigation that placing the assets in the wholly-owned subsidiaries gives BMS a beneficial entitlement to those IP assets or an equitable ownership?*

Ms Leung: *...I can't point to you a single document that says that is the case. But as I sit here and testify, I can tell you that that is my understanding. I know how the company has acted, I know what a longstanding policy is and I understand that we are, and we are in fact...owners of all the assets and can control them 100%.*

13. Ownership of Subsidiary Assets and Potential Tax Implications

163. Counsel for Teva turned next to the issues of who owns subsidiary assets and the potential tax implications of the views of BMS in this regard.

Counsel: ...[Y]*ou've explained to us that doesn't just apply to the IP asset, it applies to the other assets, isn't that correct, the same principle?*

Ms Leung: *As a principle, yes. When we acquire a company, we acquire all the assets of the company....*

Counsel: *So...once BMS Pharma was acquired on 1st October 2001, as of that date, all of the assets, not just the IP assets, were now beneficially owned by BMS?*

Ms Leung: *As at the date of the closing of the DuPont acquisition....all the assets of DuPont that were part of the transaction...we became the beneficial owners of all those assets....*

Counsel: ...[C]*an I just ask you, if the subsidiary went into bankruptcy because BMS owned those assets...they wouldn't be available for the creditors..?*

Ms Leung ....*I'm not a bankruptcy law expert, so...I won't opine on those issues....*

Counsel: *Are you suggesting, even as a lawyer with the most basic knowledge of bankruptcy and insolvency, that if an asset is beneficially owned by somebody else, it's not available to creditors? Surely you must be aware of that?*

Ms Leung: ...[A]*s I sit here now, I don't know that to be a fact. It sounds right, but I can't tell you for sure that is a fact.*

Counsel: *...BMS is regulated by the SEC, isn't that correct?*

Ms Leung: *Yes....*

Counsel: ...[W]*as the SEC ever told that the assets of the subsidiaries were beneficially owned by BMS, of the wholly-owned subsidiaries?*

Ms Leung: *I don't recall ever making such a statement to the SEC. And I think in fact...that would be a very unusual statement to make to the SEC.*

Counsel: *It would, because under American law, federal law, and under state law, the assets of a subsidiary normally belong to that subsidiary, isn't that correct?*

Ms Leung: *I don't know what you mean, belong to the subsidiary. If a subsidiary is wholly-owned by a parent...the assets...are owned by the parent.... If it's a wholly-owned subsidiary, I believe the assets -- that the parent company can control what is done with the assets of the subsidiary. All the decision-making, at least under the BMS model of wholly-owned subsidiaries is that the parent company, BMS Co, has complete control over the assets of the wholly-owned subsidiary....*

Counsel: ...[H]*ow many different countries, even just in general terms, are there located these wholly-owned subsidiaries of BMS..?*

Ms Leung: *....I can't tell you exactly.*

Counsel: *And so far as BMS is concerned, all of the assets of those wholly-owned subsidiaries are owned by BMS?*

Ms Leung: *Yes.*

Counsel: *So, if there was a company in Ireland, so far as BMS is concerned, all of its assets, if it's wholly owned directly or indirectly, are owned by BMS?*

Ms Leung: *Yes, we would be the beneficial owner and in fact we would control the decision-making of that subsidiary....*

Counsel: ...[H]*as BMS ever made a public statement or told anybody dealing with these subsidiaries that their assets are in fact only notional, because all of the assets are beneficially owned by BMS? Has that statement ever been made?*

Ms Leung: *I can't tell you as I sit here whether or not anyone has ever made that statement....*

Counsel: *Bristol-Myers Squibb Holdings Ireland, which is the patentee in this case...is earning revenue from all the sales it's engaging in, isn't that correct?*

Ms Leung: *I have no reason to believe that's not correct. I can't tell you, as I sit here now, if that...is true or not.*

Counsel: *And...benefits from Ireland's corporation tax rate, isn't that correct?*

Ms Leung: *I believe that's true.*

Counsel: *...But in fact that revenue...belongs, beneficially, to...BMS?*

Ms Leung: *If it's a wholly-owned subsidiary of BMS, the parent company, then yes, BMS Company is the owner...as I've said.*

Counsel: ...[D]*oes BMS pay tax in the US on that revenue?*

Ms Leung: *...I'm not in the Tax Department. But we do pay taxes in the US....*

Counsel: *And when you make a decision to leave a patent in a subsidiary company, you, as the expert on compliance, including SEC compliance and all other aspects of compliance and corporate governance, would be aware that decision has tax implications, isn't that correct?*

Ms Leung: *I know there are tax implications on where we hold intellectual property. But the Tax Department, the tax group would know more information.*

Counsel: *And if the IRS came to your company and said, 'We would like to see a copy of the policy that means these assets in the wholly-owned subsidiaries are assets of BMS,' there wouldn't be one document to show them, not one document?*

Ms Leung: *I'm not sure what you're asking. I've never encountered a situation that the IRS came to the company and asked to look at policies. That's not what they focus on.*

Counsel: *Well, if they came to say, 'Are these assets beneficially owned by the subsidiaries or by BMS?' There wouldn't be one document to establish that in fact they're owned by BMS.*

Ms Leung: *There's no document. But...they would certainly understand, and we'd make clear they are wholly-owned subsidiaries of Bristol-Myers Squibb Company and we control the assets of the subsidiaries.*

Counsel: ...[W]*ould you produce the e-mails of 19th and 24th October to them to substantiate your position..?*

Ms Leung: *I don't know the answer to that, because I don't know, in your*

hypothetical...what the question is and the circumstances under which it is asked....

Counsel: *But...BMS is happy to produce these two e-mails to...an Irish court, of its contention that these IP assets are beneficially owned by BMS?*

Ms Leung: *The e-mails that were produced are evidence and it's consistent with the company's longstanding policy that the IP assets of an acquired company would be held in a wholly-owned subsidiary of the company and that BMS Co would control the assets and all the decision-making with respect to those assets. So, those e-mails are consistent with that....*

Counsel: [Mr Granwell,] *a tax expert* [who]*...worked with the Government for many years, a tax expert for 43 years,* [has] *said* [in these proceedings] *that...there are significant tax consequences and regulatory consequences of a decision to place IP assets in a particular company, be it a subsidiary or a parent company. You wouldn't disagree with that..?*

Ms Leung: *I don't disagree with that. I defer to the expert on that.*

Counsel: *And therefore, any decision in respect of any particular IP assets is going to involve a consideration by the tax people and others in a company..?*

Ms Leung: *I believe that to be a true statement.*

Counsel: *...And when the asset is placed in a particular subsidiary, that is a deliberate decision to do so?*

Ms Leung: *...I believe that is true....*

Counsel: *...*[D]*id you ever get any advice in Ireland as to whether exercising direct control was sufficient to preserve or give beneficial interest to BMS?*

Ms Leung: *I did not....*

Counsel: *Or did you get advice in any of the other 40-odd countries as to what the legal position was?*

Ms Leung: *I did not....We're a Delaware corporation.*

Counsel: *...*[T]*he issue of beneficial ownership of assets of a company registered in Ireland would...be determined by Irish law, isn't that correct?*

Ms Leung: *I believe that is correct. And I rely on our counsel in Ireland...to make these determinations. I personally did not seek an opinion.*

Counsel: *...*[H]*as any of them ever furnished to you an opinion suggesting that the assets of these subsidiaries are not beneficially owned by the subsidiaries?*

Ms Leung: *No.*

Counsel: *....So, the whole of BMS policy, its whole protection of its IP assets, is based on a statement as to beneficial ownership that is not supported by any opinion, is not considered in the context of any individual country, save the State of Delaware..?*

Ms Leung: *....I don't have an opinion from counsel in Ireland or any other country with respect to the definition of beneficial ownership or whether or not beneficial ownership was established. What I do rely on is my many years of experience and the longstanding practice of BMS.*

Counsel: *And if that be so, if...all of the revenue in these countries...generated by these beneficially owned assets is revenue of BMS, that would have very significant consequences for BMS, isn't that correct?*

Ms Leung: *I believe that to be a true statement....*

14. Corporate Separateness

164. Counsel for Teva turned next to explore with Ms Leung the matter of corporate separateness:

Counsel:	*Ms Leung, when you were making your statement about beneficial interest, did you take into account the principle of corporate separateness? ...*
Ms Leung:	*I didn't specifically take it into account, because I didn't view it as an issue of corporate veil piercing, which I understand is the concept here.*
Counsel:	....[C]*orporate veil piercing occurs where two corporations are effectively indistinguishable..?*
Ms Leung:	*I think that...to pierce a corporate veil is to hold the parent company or subsidiary liable for the acts alleged against one of them....*
Counsel:	...[I]*t's one of the exceptions to corporate separateness..?*
Ms Leung:	*Without getting deep into understanding Delaware law and corporate veil piercing, I have no reason to believe what you say is not true....*
Counsel:	...[V]*eil piercing is done where there's evidence of fraud...or...serious wrongdoing..?*
Ms Leung:	*It could be raised in a number of contexts, but I believe that...it's often raised when there is an allegation of wrongdoing.*
Counsel:	*And there's no suggestion here of any allegation of wrongdoing so far as BMS or its subsidiary is concerned..?*
Ms Leung:	*....Not that I am aware of....*
Counsel:	*Are you aware that the only exceptions* [in Delaware law] *to corporate separateness that are clearly established are...sections 220 and 271 of the Delaware Corporate Code and the appraisal statute?*
Ms Leung:	*I am not an expert in Delaware law,* [so] *I don't know the specific statute references to Delaware law that you're stating and I would* [leave such matters]*...to the Delaware law experts...in this trial.*

15. The Assignments in this Case

165. Counsel for Teva turned next to the assignments that were effected in this matter. He noted that the assignment of 23rd April 2007, amongst other matters, "*does hereby assign to the assignee the entire right, title and interest in all countries of the world in and to* [patent application '165]". Ms Leung indicated in this regard that this "*was a standard form that was used and it's not unusual in these assignments, in an excess of caution, to put in any and all rights, even if....the person assigning it doesn't necessarily hold it. Because you can't...assign rights you don't have.*"

166. When counsel put it to Ms Leung that in an SEC regulated company "*words on a page of formal and important documents matter*", Ms Leung indicated that this is so "[b]*ut again, it's understood that these are likely forms and an assignor can't assign any rights they don't have*".

167. When counsel put it to Ms Leung that the assignment later moves on to assign "*any remaining right, title and interest in all countries of the world in and to any patent application claiming priority from said patent application* [165]", counsel suggesting as follows in this regard: "*So, where it wants to assign remaining rights, it distinguishes that and says that…'?*" To this, Ms Leung responded in a similar vein, observing that the assignment:

"...says any remaining rights...for any avoidance of doubt, because you never know

what allegation or issues might be raised in the future....So, this is a very cautious, complete approach, belt and suspenders, kitchen sink, everything thrown in there....I think in this specific case there was a...specific reference, to the patent application. And that's what it clearly says here. And it is...common practice, to put in specifically something and then cover anything else that might arise in an excess of caution."

168. Counsel looked next to the assignment of 2016, noting how it states "*Assignor hereby confirms that (i) it previously sold, assigned, transferred and delivered to Assignee, and Assignee accepted all of the rights, title and interest in, to and under the Assigned Patents*". At this point the following exchange occurred between counsel and Ms Leung:

Counsel:	*There, we have a confirmation...*[of the previous]*...assignment...*
Ms Leung:	*Yes....*
Counsel:	*So, when something has already been assigned, the drafters just confirm that assignment?*
Ms Leung:	*....*[A]*gain, in an excess of cautions, for avoidance of doubt.*
Counsel:	*So, they confirm where they believe there's already been an assignment..?*
Ms Leung:	*This is a confirmatory assignment, as I understand it.*
Counsel:	*....But that's not what was done in 2007.*
Ms Leung:	*The 2007 Assignment was done, as I understand it...in a different context. And so I don't...read anything into the fact that one is confirmatory and one is not, because the underlying facts are BMS Company controlled completely the IP assets that were formerly owned by the former DuPont company.*

169. The 2007 Assignment, as I understand matters, was done in the context of the expected commercialisation of Eliquis. As part of that process, Pfizer requested that BMS provide information regarding the chain of title for the apixaban patent applications and patents and a copy of the IP transfer agreement between DuPont Pharma and BMS. Ms Leung saw nothing untoward in this process, observing at one point, in response to questions from counsel for Teva:

"*I don't recall if Pfizer raised a specific issue. This is common practice in transactions like the one we have with Pfizer where, during the diligence process, you look, you raise all kinds of issues relating to this. And this is also a situation too where we wanted to be – where we were very clear. And it's another belt and suspenders approach*",

and, at a later stage:

"*Again, I view this as not unusual. During diligence, you wanted belt and suspenders tick and tie everything for avoidance of doubt*",

and, still later, the following exchange occurred between Ms Leung and counsel for Teva:

Ms Leung:	*I think* [the] *2007* [assignment] *was prepared in the context of anticipated commercialisation of Eliquis to respond to our partner's request for belt and suspenders. And frankly, I'm not surprised by that at all; we probably would've asked for the same thing, just for avoidance of any doubt.*
Counsel:	*But on its face, the conveyance of the entire right, on its face, the words used are inconsistent with a beneficial right already being in –*
Ms Leung:	*No, I don't think it's inconsistent at all....*[b]*ecause you can't give rights that you don't have. And this was being –*

Counsel: *No, but the words used in the document. If I say to you 'I consign the entire right', it purports to say - it may not in fact be true - that I have the entire right to assign. That's what it purports to say.*

Ms Leung: *I don't dispute the words on the assignment itself. But in the context in which this assignment was made, it was clear that BMS...exercised complete control over the IP of DuPont*".

170. In its closing written submissions, Teva again returns to the point that Pfizer enquired of BMS as to the chain of title for the apixaban patent applications and patents, noting that: (i) in an email of 26th March 2007, Pfizer wrote in the following terms to BMS:

"***I would like to discuss the chain of title concerning US provisional applications 60/324,165*** *... . Ideally I would like to view the agreement (IP transfer or other possible type) between DuPont and BMS transferring rights, if any, regarding the previously listed patents and patent applications."*

[Teva's emphasis]

171. I note that my attention is drawn, through the use of Bold, underlined text, to the first of the two sentences. But the second of the two sentences seems to me to be of more significance, for it states that "*Ideally I would like to view the agreement...if any*". In this Pfizer seems to me to be suggesting that there are other means of enjoying ownership than by way of a written agreement. So although the email is offered as chiming with Teva's 'assignment good, no assignment bad' logic, in fact it does not seem on its face to support this argument. The point is a minor one in the grand scheme of things: it matters nought what Pfizer thought; its views are not determinative of whether or not BMS owns the assets that it owns.

172. Counsel for Teva also drew Ms Leung's attention to the comment made by an unknown individual, most likely a lawyer, in respect of the sentence "*Assignors covenant that assignor had or has the right to enter into the patent agreement*". The comment read "*Otherwise, BMS Pharma Co is covenanting that they still own the patents even after the 2007 Assignment right? Or is it fine as is because they still have the right to confirm what they've already done?*" Ms Leung, as I half-expected, responded in this regard that *"I see the comment made by someone. I don't know who it is, I don't know what the person's background was, I don't know if they understood the DuPont transaction or what had happened before. So I have no idea who that person is....So I can't tell you whether the person knew or didn't know.*" In truth, at this stage it was little better than a piece of graffiti by an unknown individual. In any event this was one of the final points in the exchange between counsel for Teva and Ms Leung on her first day in the witness box and led on to the following (ostensibly final) exchange:

Counsel: *I have to suggest to you...that this theory now being advanced by BMS of a beneficial interest existing in these assets is something that was not part of the policy at the time...that it wasn't BMS's understanding at the time, that BMS did not act on that basis and that this was something belatedly thought of after it was discovered that there was no assignment.*

Ms Leung: *I disagree completely with you.*

Counsel: *And that no such policies exists of the type that you have suggested?*

Ms Leung: *I can tell you that I have been at the company for 31 years and that is the policy of the company.*

173. . Ms Leung at all times adhered to what I believe (having heard and read all the evidence before me) to be the truth, namely that for years BMS has adhered to a general policy in which, when it acquires companies, it tends to leave their patents in a wholly owned subsidiary company, to which

it appoints BMS staff as directors and officers (who in a Delaware company have a duty to make decisions in the best interests of the parent company, here BMS).

16. BMS Ireland Unlimited Company

174. Though he appeared to have ended his cross-examination on the first day that Ms Leung was in the witness-box, counsel for Teva asked and was allowed to return to his cross-examination, to focus in on the points that Ms Leung had made concerning the ownership of subsidiary assets, most notably in Ireland. I will proceed now to consider that additional evidence. However, I should note that the fact that Ms Leung, in the course of a protracted cross-examination (and doubtless when she was quite exhausted by the vigour and length of the questioning) initially offered a particular view as to the ownership of subsidiary assets, most notably in Ireland, does nothing to affect how Delaware law in fact operates *vis-à-vis* BMS Co. and BMS Pharma. In short, much of the questioning that I now proceed to describe had no relevance in terms of my deciding the issues that it has actually fallen to me to decide.

175. Counsel for Teva began by bringing Ms Leung to the 2021 financial statements of the above-named company, including the statement by the directors of their responsibilities, and the mention therein that:

> "*The company is an indirect wholly-owned subsidiary of Bristol-Myers Squibb Company, its ultimate parent company. It is an Irish incorporated company with its head office in Switzerland. The principal activity of the company is to act as a holding company for Bristol-Myers Squibb Group companies. In addition, the company owns and manages selected non-US intellectual property rights for certain pharmaceutical products*",
>
> and later that:
>
> "*The company holds the rights for certain intellectual property for pharmaceutical products. It is exposed to economic and market conditions in which these products are sold, along with a risk of exclusivity earlier than envisaged due to patent litigation*",
>
> and later that:
>
> "*The company is an indirect wholly-owned subsidiary of Bristol-Myers Squibb, the ultimate parent company. It is an Irish incorporated company with registered number... and its activity is act as holding company for Bristol-Myers Squibb Group companies.*"

176. Among the exchanges between counsel and Ms Leung at this juncture were the following:

> Ms Leung: ...[W]*hat the document reads...is consistent with the statement I made yesterday that in certain circumstances...there may be exceptions to the general statement that I made....So, there are special circumstances. And as I testified yesterday, I did not recall, given the lateness of the hour and the activities of the day, that Bristol-Myers Squibb Holdings Ireland Unlimited Company is one of those special situations.*
>
> Counsel: *Ms Leung, your evidence yesterday was very particular; that they did own the assets of the Irish companies....*[and that] *the revenue belonged to BMS. That was very specific evidence you gave.*
>
> Ms Leung: *When...I testified to that yesterday, we had been speaking with respect of beneficial ownership. In reviewing these documents today and familiarising myself with Bristol-Myers Squibb*

Holdings Ireland Unlimited Company, I fully understand that ownership of intangible assets does not necessarily drive where income derived from those assets should be allocated, so those were different situations....[T]*hose things you just brought my attention to are consistent with the statement I made yesterday that...when there are special situations and a business need...there may be differences....*

Counsel: *So, all of these intellectual property assets are held by the Irish company, isn't that correct? And they're the beneficial owner of those assets?*

Ms Leung: *Yes, but this special situation with Bristol-Myers Squibb Holdings Ireland Unlimited Company, that is true.*

Counsel: [after reading out relevant extracts from Ms Leung's evidence of the previous day] *...Do you think that's consistent with what's in this document* [the financial statements]..?

Ms Leung: *....I don't have the transcript in front of me, but I can tell you today, and my testimony is, with respect to Bristol-Myers Squibb Holdings Ireland, that is one of the special situations that I discussed yesterday where we may not treat it as we do the vast majority of our wholly-owned subsidiaries. There is apparently a business purpose in treating Bristol-Myers Squibb Holdings Ireland differently than how we treated the other subsidiaries of the company.*

Counsel: *And you see that Bristol-Myers Squibb Ireland has no employees..?*

Ms Leung: *...I believe that in this special situation...there are employees of Bristol-Myers Squibb Ireland who are either employed by BMS Co or a wholly-owned subsidiary of BMS Co....*

Counsel: [The] *patent department in BMS Company makes all the decisions, controls and directs the handling of these patents, isn't that correct?*

Ms Leung: *They provide advice and I believe they do....*

Counsel: *....The directors are not employees of the company, they're...employed by group companies. That was the same position with BMS Pharma..?*

Ms Leung: *That's correct.*

Counsel: *And BMS Pharma, you said, had no employees?*

Ms Leung: *BMS Pharma had no employees, that's correct....*

Counsel: *Services to it were provided by Group companies..?*

Ms Leung: *It was provided by employees of BMS Company or a wholly-owned subsidiary of BMS Co.*

Counsel: *So, all matters relating to this company are done or directed from BMS Company or some other group company..?*

Ms Leung: *By group company if you mean* [the] *wholly-owned subsidiary Bristol-Myers Squibb, yes, that's correct.*

Counsel: *Yet, in this case, you accept that BMS does not have any beneficial interest in these assets?*

Ms Leung *I don't know, because this is a special situation with Bristol-Myers Squibb Holdings Ireland, with respect to beneficial ownership....*

Counsel: *And I take it you would accept, at face value, that these directors say that they discharged their duties and have meetings from time to time; would you accept that?*

Ms Leung: *I have no reason to think they did not.*

Counsel: *And I suggest that in any of the group companies in the BMS structure, even though the directors may be employees of BMS Company or other companies, they do perform their statutory or*

legal obligations.

Ms Leung: *They comply with all requirements in the jurisdiction in which they are formed and required by law. So, that is my response, that I would expect that they fulfil their obligations and comply with laws and obligations that are applicable.*

Counsel: *And that is the same in the US, isn't it? Its subsidiaries and the Board of Directors comply with the relevant laws, isn't that correct?*

Ms Leung: *Yes.*

Counsel: *And they would hold meetings and do whatever else they are required to do in accordance with law?*

Ms Leung: *If they were required by law, yes, they would.*

Counsel: *And the same applies to BMS Pharma, isn't that correct?*

Ms Leung: *I would assume that is true. But BMS Pharma, again, is a wholly-owned subsidiary of BMS Co. But if there were other requirements, it would comply with all laws and requirements.*

177. I cannot but respectfully note that while Ms Leung is clearly a competent professional and proved in the witness box to be an accomplished witness, her views on the ownership of subsidiary assets, with respect, are not determinative as a matter of Delaware law (the applicable law when it comes to BMS Company and BMS Pharma) and, indeed, she was careful in her oral evidence not to hold herself out as an expert on Delaware law.

17. BMS's International Tax Affairs

178. In a further line of questioning, counsel for Teva next brought Ms Leung to newspaper reportage from 2021 in which the *New York Times* recounted certain tax difficulties that BMS seems to have encountered around that time concerning its international tax arrangements. Counsel for Teva emphasised that he was not suggesting there to have been any impropriety on the part of BMS in this regard. What he noted from this reportage was that various BMS subsidiaries "*in...different jurisdictions owned the legal and beneficial interest in those patents*" and suggested to Ms Leung that "*your evidence of yesterday with respect to how BMS controlled its subsidiaries and owned the assets of these subsidiaries...is not correct and that the proposition you have put forward in relation to control and ownership in respect of these subsidiaries, including BMS Pharma, is incorrect.*" To this, Ms Leung responded that "*I vehemently disagree with you on that point. As I testified yesterday, there could be special situations, as apparently BMS Ireland Holdings is one of them, where we may have taken a different approach, again for good business reasons.*"

179. Again, I cannot but respectfully note that while Ms Leung is clearly a competent professional and proved in the witness box to be an accomplished witness, her views on the ownership of subsidiary assets, with respect, are not determinative as a matter of Delaware law (the applicable law when it comes to BMS Company and BMS Pharma) and, indeed, she was careful in her oral evidence not to hold herself out as an expert on Delaware law.

18. BMS's Allegedly Changing Case

180. In his closing submissions, counsel for Teva suggested that Ms Leung's evidence concerning subsidiary assets (including the assets of BMS Ireland Unlimited Company) was an example of how BMS has constantly changed its case even in the course of proceedings. In its closing written submissions Teva refers to this as "*an overnight volte face*", observing as follows:

"*3.55* *On Day 10, Ms Leung confirmed that her general position of global, beneficial ownership applied to the assets of BMS Ireland specifically, including expressly the patent in suit....*

3.56 *On the same legal theory, Ms Leung likewise asserted that BMS Co. owned of*

BMS Ireland's income stream. She allowed that, "if there were good business reasons to make a different decision in the exercise of our central, complete and unfettered control of the assets of the acquired company, it was in our -- we could have made a different decision."

3.57 However, overnight, Ms Leung was furnished with the Directors' Report and Audited Financial Statements for BMS Ireland which stated, 'In addition, the Company owns and manages selected non-US intellectual property rights for certain pharmaceutical products.' The Profit and Loss Account at page 9 of the Financial Statements reflects significant income accruing to BMS Ireland and a profit of $4,603,084,000.

3.58 Having reviewed those materials, Ms Leung now stated that BMS Co. did not actually own the assets or income stream of BMS Ireland, stating:

> *'And this is consistent with the statement I made yesterday that in certain circumstances where there are substantial, significant business needs, there may be exceptions to the general statement that I made that wholly owned subsidiary, that the responsibility of the directors, that wholly owned subsidiaries don't have employees and things of that sort. So, there are special circumstances. And as I testified yesterday, I did not recall, given the lateness of the hour and the activities of the day, that Bristol-Myers Squibb Holdings Ireland Unlimited Company is one of those special situations.'*

3.59 This was notwithstanding Ms Leung's confirmations that BMS Ireland, just like BMS Pharma, has no employees, its directors are employed by BMS Co. or another wholly owned subsidiary, and it is advised by the patent department of BMS Company.

3.60 It is entirely implausible that BMS asserts ownership over all or practically all of its subsidiaries, worldwide, and their assets, of any sort, for the purposes of these proceedings on an undocumented 'legal theory' of beneficial ownership, but (in identical circumstances) carves out an exception overnight for a 'special situation with Bristol-Myers Squibb Holdings Ireland, with respect to beneficial ownership.'"

181. Three points might be made in this regard. First, in the above-quoted text Teva focuses in on certain observations made late in the day by a witness who had endured several hours of protracted and vigorous cross-examination and who subsequently corrected/clarified herself at the earliest opportunity. Second, while Ms Leung is (if I might, again respectfully, observe) clearly a talented professional and proved in the witness box to be an accomplished witness, her views on the ownership of subsidiary assets are not determinative as a matter of Delaware law (the applicable law when it comes to BMS Company and BMS Pharma) and, indeed, she was careful in her oral evidence not to hold herself out as an expert on Delaware law. Third, my focus in these proceedings is on the proposition (which is correct per the Common Delaware Evidence) that the level of control exercised by BMS Company vis-à-vis BMS Pharma was such that under Delaware law, and by operation of the law of that jurisdiction, BMS Co would be held to be the beneficial owner of US165. If by holding that proposition, as proffered by BMS, to be correct, I cause some other problem for BMS in terms of what it owns in Ireland or elsewhere (or on what basis) then that is for BMS and/or some future judge to resolve, not me.

182. It should not be taken in anything that I have stated in the preceding paragraph to accept the proposition (for I do not accept the proposition) that BMS has constantly sought to change its case in these proceedings. I have explained in some detail in chapter 2 why I do not consider that this is so. Again, the fact that one witness, who was careful in her oral evidence not to hold herself out as an expert on Delaware law, should offer in the course of her evidence (after enduring several hours

of protracted and vigorous cross-examination) a view as to the ownership of subsidiary assets which she corrected/clarified at the earliest opportunity is, frankly (and with all due respect to Ms Leung) not determinative as a matter of Delaware law (the applicable law when it comes to BMS Company and BMS Pharma) and, indeed, she was careful in her oral evidence not to hold herself out as an expert on Delaware law.

D. Re-Examination

1. Nomination of Directors and Officers of New BMS Entities

183. Counsel for BMS brought Ms Leung to her emails of 24th October 2001 concerning the nomination of directors and officers of new BMS entities and asked her what was afoot in these emails. To this, Ms Leung responded that "[A]*gain, this is standard practice...for situations where we acquire a new company. We wanted to be sure that we are in a position to establish BMS Pharma Company with employees of BMS Co, listing all the directors and officers who were employees of BMS Co. And this was in anticipation of the filings that we needed to make in the State of Delaware to establish the subsidiary.*"

184. Asked why was it the practice of BMS Co to replace the directors and executive officers of companies it was acquiring, Ms Leung indicated that "[I]*t was to be clear that we, Bristol-Myers Squibb Company, own the assets of the new company and we didn't want there to be any ambiguity with respect to that. And again, this was standard, longstanding practice at BMS in an acquisition situation.*"

185. Asked to confirm that the listed directors/officers were all employees of BMS Co., Ms Leung indicated that "*I know each and every person who is listed in this company.*"

2. Steps Taken Pre-Acquisition to Ensure Post-Acquisition Control

186. Referring to the fact that counsel for Teva had challenged Ms Leung's evidence in relation to control, both in chief and upon cross-examination, counsel for BMS asked Ms Leung to respond to that in the context of the steps that she took in August 2001 (pre-acquisition). To this, Ms Leung responded that "[A]*ll the steps that we took in that timeframe in August of 2001 in anticipation of the closing of the DuPont acquisition were in furtherance of gaining control and exercising complete control over the assets that we acquired from DuPont.*"

3. Date of Establishment of BMS Ireland Limited Company

187. Counsel for BMS brought Ms Leung to the financial statements of BMS Ireland Unlimited Company and asked Ms Leung to confirm the date of incorporation of that company (2nd September 2002), *i.e.* almost 12 months after the DuPont acquisition.

4. The *New York Times* Reportage

188. In a similar vein, counsel for BMS elicited from Ms Leung that the tax structure at the heart of the *New York Times* reportage was established in or about 2012.

189. In her later evidence, while under re-examination, Ms Leung also indicated of the matter the subject of the *New York Times* reportage that "[I]*t's ongoing with the IRS...*[I]*t's something that we reference from time to time in our periodic filings with the SEC...*[T]*hat's how I'm aware of it....*[I]*t has not been resolved*", still later confirming that a determination made by the IRS in this context is the subject of ongoing challenge.

5. Exceptions to the General Approach of BMS Company as Regards Subsidiaries

190. Counsel for BMS turned next to the issue of exceptions to BMS's general approach as regards subsidiaries. In this regard, counsel brought Ms Leung to point (3) of the Francis Rossi email of 24th October 2001, where the following is stated:

> "*(3) Patents and trademarks related to the CombiChem (DPRL) business. This business is expected to be sold very soon, therefore all trademarks and all patents related to the business – to the extent they will be included in the sale – should be assigned to the entity, Bristol-Myers Squibb Pharma Research Labs, Inc. (formerly DuPont Pharmaceutical Research Labs, Inc., and before that, CombiChem). Apparently at least some of the intangibles are registered in the name of Combichem – and it is my understanding from representations DuPont tax made in due diligence that DPRL is the same legal entity as Combichem. I spoke with Doug Worthington, who is the legal counsel working on this disposition, and he indicated that decisions are being made regarding which patents and other intangibles are going to be sold with the business, since we may retain some – so any transfers should be coordinated with him. Any intangibles not transferred with the business should stay at BMSPC.*"

191. The following exchange occurred between counsel for BMS and Ms Leung in this last regard:

Counsel:	...[Y]*esterday it was stated by you on a number of occasions about exceptions to the approach of Bristol-Myers Squibb Company?*
Ms Leung:	*Yes.*
Counsel:	*And there could be exceptional circumstances justified by reference to business reasons, and you referred this morning to Holdings being one of those. But can I ask you to look at...the* [Francis Rossi] *e-mail of 24th October 2001?*
Ms Leung:	*Yes, I have that.*
Counsel:	*And can I just ask you to comment on....the entity referred to in paragraph number 3 and the suggestion that there should be assignments of certain patents to that entity? Can you just talk to the court about that?*
Ms Leung:	...[P]*aragraph 3 relates to CombiChem. It's a business that we acquired from DuPont....[A]s the e-mail indicates, the business was expected to be sold very soon and, therefore, the direction was that all trademarks and patents related to the business, to the extent they will be included in the sale, should be assigned to a different entity, and that different entity was Bristol-Myers Squibb Pharma Research Labs. And that was the successor corporation, it used to be DuPont Pharmaceutical Research Labs, and before that CombiChem. And it goes on to say that '...at least some of the intangibles are still registered in the name of CombiChem...'. And the writer, Margaret Yonco-Haines [whose email is the principal email in the chain, with Mr Rossi forwarding it to others], says that's what she understands from the tax department of DuPont. And she also indicates that DuPont tax represented BMS during diligence that DPRL – or that's the DuPont Pharmaceutical Research Labs - is the same legal entity as CombiChem. So, this is a situation, another one of those special situations where something different was done with the IP and the assets in a situation where this particular business was being set up to be sold. So, this made it – that was another business purpose where we took a different position than our normal position, for good business reasons.*

6. Absence of Mr Ferguson

192. Counsel for BMS noted that counsel for Teva had asked a number of times about why Mr. Blair Ferguson was not giving evidence in these proceedings and whether he had been asked to give evidence. Counsel then asked Ms Leung whether she knew "*that it has been deposed to on affidavit in this case that when Blair Ferguson was approached, he had no recollection of any of the issues or events going back to 2001 and 2002*". To this, Ms Leung responded that she was not aware "*that someone had spoken to him and* [that] *he said that he had no recollection.*"

7. Ms Leung's Role in BMS

193. Through a series of questions, counsel for BMS elicited the following information from Ms Leung:

(i) there are over 200 lawyers globally who report ultimately to Ms Leung, in addition to outside counsel.

(ii) as general counsel of BMS Co, Ms Leung is not intimately involved in, or familiar with, the day-to-day management of litigation. "*Not the day-to-day management. I do have a Head of Litigation who is involved with the day-to-day aspects, along with his team of lawyers who deal with it. We have approximately six lawyers who deal with litigation, perhaps more.*" (Again, this is in addition to external counsel.)

(iii) Ms Leung would expect outside and internal counsel to identify relevant information and provide that;

(iv) Ms Leung had no idea what Judge Holland was told, because she was not involved in instructing Judge Holland;

(v) in the context of Judge Holland's instructions, Ms Leung (i) thought that a bona fide, diligent effort was made to look for the assignments; (ii) also indicated to counsel for BMS that "*I don't know the details, I wasn't involved in the discovery phase and turning over documents, so I can't tell you from firsthand knowledge.*"

(vi) aside from not being involved in discovery in that case, Ms Leung would not be involved in collecting documents for discovery in any of the litigation? "*I would not be involved in that. There are many people who would take on that role. If I did that, I think my Board of Directors and my CEO would believe that is not a good use of my time.*"

(vii) Ms Leung learned "*very recently*" that there was a dispute with respect to discovery in these proceedings.

(viii) after an exchange in which counsel for BMS divulged that certain later documents, including the Blair Ferguson e-mails and manuals, were first identified as relevant in January 2023, Ms Leung indicated that she would not have gone out and found the Blair Ferguson e-mail and manual before Scott Brown and McCann FitzGerald identified it as a relevant document;

(ix) returning to the email of 24th October 2001 and the recommendation therein that (a) "*Patents and trademarks related to the Pharmaceutical business - Maintain legal ownership in Bristol-Myers Squibb Pharma Company (formerly DPC)*", that this was in fact what had occurred vis-à-vis Application '165, (b) *"New patents and trademarks* [should be] *in the name of Bristol-Myers Squibb Company*", this was the company in which the later patent was filed;

(x) as regards the e-mail from Blair Ferguson dated 30th January, 2002, this was the email to which Ms Leung "*was referring to where direction was not followed*";

(xi) Ms Leung's understanding is that by the time Judge Holland provided his evidence, "*we have*" (I believe this means 'BMS had') three assignments but

Ms Leung was not involved in relation to trying to find assignments;

(xii) as regards the 2007 Assignment, Ms Leung saw no significant difference between the wording therein *("does hereby assign to assignee the entire right, title and interest in all countries of the world in and to the patent application ...165...and any remaining right, title and interest in all countries of the world*") and the related wording in the inventor assignment ("[s]*ell, assign and transfer...(A) the sole and entire right, and interest in and to (1) the aforesaid application for Letters Patent, (2) any priority rights derived*");

(xiii) as to the Mathias statement and the reference therein to its being "*a no-brainer to leave them where they were as we had access to them anyway so why go the effort of assigning them? There was no need to transfer legal title*", the only reference made by Ms Matthias is to legal title; and

(xiv) as to the mention of beneficial interest in Ms Leung's statement of August 2022, Ms Leung believed that the concept of beneficial interest was expressly referred to in the pleadings in this case in January 2022.

6

The Evidence of Mr Golian

A. Introduction

194. Mr Golian is a patent attorney. He joined BMS on 1st July 2002 and since then has taken an increased responsibility, handling all aspects of patent law. I turn now to consider the oral testimony of Mr Golian. Subject to para.4 of this judgment, an abridged version of his previous written evidence is set out at Appendix 5. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

B. Examination

1. Management of BMS Pharma and other BMS Subsidiaries

195. Asked by counsel for BMS who was making the decision in relation to (i) BMS Pharma's intellectual property, and (ii) the management of same, when he joined BMS, Mr Golian indicated as follows:

> "[A]*s you just stated, BMS Pharma did not have its own employees. So, for example, when I joined in July 2002, I was employed by BMS Co, not BMS Pharma. And the lawyers and other advisers in relation to BMS Pharma patent matters resided with BMS Company.*"

196. Mr Golian was brought by counsel for BMS to the section of his witness statement in which he states as follows:

> "*The 24th October 2001 email reflects decision making by BMS Co as to the legal ownership of Bristol Myers Squibb Pharma Company's intellectual property, and the putting in place of policy in that regard, consistent with my experience of BMS Co being the decision maker and having control over how intellectual property assets of its wholly owned subsidiaries are to be held*".

197. Asked by counsel for BMS if that approach was adopted in respect of patents held by other subsidiaries as acquired companies. Mr Golian indicated that it was.

2. Corporate Governance

198. I asked Mr Golian "*In terms of good corporate governance, how does a policy get approved in BMS? Does it go to the executive team or does it go to the Board or how does it happen?*". To this, Mr Golian responded as follows:

> "*So, I would say when I joined BMS in July 2002, there was a pre-existing practice of, from time to time, BMS would acquire other companies and the practice was, generally speaking, that that newly acquired company would become a subsidiary of BMS Company. And just as we had here with what became BMS Pharma, it would be BMS Co that would make decisions with respect to, not only intellectual property, but other aspects of managing that newly acquired company.*"

C. Cross- Examination

1. Role of Mr Golian

199. Counsel for Teva asked Mr Golian if his role at BMS includes filing patent applications Mr Golian indicated that it does.

2. Patent Attorney as Agent

200. Counsel for Teva asked of Mr Golian what it means where, on a PCT application, a patent attorney is named as agent for the applicant. In response, Mr Golian indicated that "*It generally means that that patent attorney filed the PCT patent application*" and would be responsible for the contents of same.

3. Non- involvement of Mr Golian in Certain Key Matters

201. Mr Golian confirmed that (i) the October 2001 emails pre-date his joining BMS as an employee, (ii) he was not involved in the 2007 assignment and (iii) he did not handle any of the particular intellectual property rights in issue in these proceedings.

4. Inventor Role

202. Turning to the inventors' role in the patent process, the following exchange occurred between counsel for Teva and Mr Golian:

Counsel:	*...I just want to ask you then, Mr. Golian, some questions about the chain of title in relation to US 165. First of all… can I ask you to agree that US 165… was filed in the names of the inventors, Mr Pinto and Ms. Quan?*
Mr Golian:	*That's correct.*
Counsel:	*And do you accept, therefore, that the inventors had the right to claim priority from US 165?*
Mr Golian:	*I believe what occurred first was the application was filed in the name of the two inventors and then the next event was an assignment from the inventors to BMS Pharma.*
Counsel:	*That's a correct statement of the chronology, Mr. Golian. And can I ask you, therefore, to agree with me that between the application in September 2001 and the assignment by the inventors in November 2001, that in that period the inventors enjoyed the right to claim priority under US 165?*
Mr Golian:	*I think we should look at the employment agreements and determine whether the employment agreements gave the inventors certain rights….*[T]*he patent application, it's a common practice in the US, was filed in the name of the inventors, but it was at a time that DuPont Pharma was the employer of the inventors.*

203. At this point counsel for Teva referred Mr Golian to the reply in the pleadings where it is admitted "*that the right to claim priority from US 165 vested jointly in Drs Pinto and Quan as the persons in whose names US 165 was filed.*" Asked if he agreed with this reply, Mr Golian indicated that he did.

204. Counsel for Teva turned next to the substance of the inventor assignment, at which point the following exchange occurred between counsel and Mr Golian:

Counsel:	...[T]*his is the inventors' assignment....*[C]*an I ask you to consider the operative clause which begins at I whereby the inventors: 'Sell, assign and transfer unto Bristol Myers Squibb Pharma Company Pharma...' And you'll see there that it's a general partnership. Do you agree that BMS Pharma is a general partnership…?*
Mr Golian:	*...I don't have any reason to believe that BMS Pharma is not a general partnership.*
Counsel:	[W]*hat's assigned then is: 'The sole and entire right, and interest in and to: (1) the aforesaid application for Letters Patent...'...*[being] *US 165, isn't that right?*
Mr Golian:	*It is.*
Counsel:	….[D]*o you agree with me that that assignment indicates that the assignors at that time enjoyed the sole and entire right and interest in and to US 165?*
Mr Golian:	[T]*his is a template assignment and would include general language….I would say that this is an assignment of the legal title of US 165 from the inventors to BMS Pharma….*
Counsel:	[C]*an you direct me to where, in this assignment, it's confined to legal title only?*
Mr Golian:	*I cannot.*
Counsel:	...[S]*o when you see the terms "the sole and entire right and interest in and to", you disagree that that includes legal and equitable title, do you?*
Mr Golian:	*I would say that well... I think that this actually is granting both legal and beneficial or equitable title….I'm sorry, I misspoke. I do see in paragraph II that the inventors are giving to the assignee, BMS Pharma, certain rights as specified in paragraph II….I would say that what the inventors are doing here is they're assigning the rights that they have. And this is a template form…*
Judge:	*So, you're saying they're assigning all they can and that they're not assigning everything under the sun, is that it?*
Mr Golian:	*I'm saying that …. while this document indicates that they are assigning everything under the sun, that doesn't necessarily mean that they have all of those rights….For example, I view this document as their assigning legal title but not necessarily other rights, including necessarily having beneficial interest….*[M]*y evidence here is, under this assignment, the inventors are assigning to BMS Pharma the rights that they have. And I think this topic of beneficial title is for experts under Delaware law to opine on. But it would be my understanding that BMS Company is controlling, at this time, the intellectual property assets of BMS Pharma, and this assignment was executed for that reason.*

205. Pressed on his initial evidence that "*I would say that this is an assignment from the inventors to BMS Pharma with respect to both legal and beneficial title of US 165*", Mr Golian indicated that this did not remain his evidence, saying, "*I've reviewed lots of documents, so I was a little unsure. So, I think this is an assignment, just to be clear, this is an assignment from the inventors to BMS Pharma of the rights that the inventors possessed in US 165.*"

5. Role of BMS Company

i. Decisions re. US 165 post assignment of 2001

206. Asked by counsel for Teva whether he could identify any decisions taken by BMS Company in relation to this patent post- assignment Mr Golian indicated that "[A]*fter this assignment of*

November 2001, we have BMS Company taking responsibility for US 165 and the next patent filing was the PCT equivalent – PCT application WO652. So that was a patent filing done by BMS Co."

ii. Role of BMS Company pre-3rd November 2001

[It will be recalled that this is the date of the assignment of the inventor rights to BMS Pharma.]

207. Asked by counsel for Teva what he had to say in relation to whether BMS Company was, prior to 3rd November 2001 making decisions for BMS in relation to the 652 application, the following exchange occurred between Mr Golian and counsel:

Mr Golian:	*I think effective October of 2001, BMS Company was integrating DuPont Pharma and was beginning to take actions with respect to that integration.*
Counsel:	*Did BMS Company have control of BMS Pharma from 1 October, 2001?*
Mr Golian:	*I think with the acquisition of DuPont Pharma, there was an entity, BMS Pharma, that was a wholly owned subsidiary of BMS Company. And the decision was made that BMS Company would control the business activities of what was now BMS Pharma, including with respect to patent matters.*

iii. Assignment to BMS Company, rather than BMS Pharma

208. Asked by counsel for Teva whether BMS Company could have required the inventors to assign their priority rights to BMS Company, rather than BMS Pharma, Mr Golian observed that "*I think BMS Company was deciding what to do … and made the decision here that* [in] *this assignment dated November 3, 2001, the inventors would assign to BMS Pharma.*"

209. Asked by counsel for Teva if this was a decision by BMS Company, Mr Golian observed as follows:

> "*I think that BMS Company was taking over from a patent application that predated the acquisition and it's ultimately BMS now putting into action an assignment for a patent application* [this is the 3rd November assignment] *that had been filed before the acquisition closed.*"

iv. Compulsion of Inventor Assignment

210. Asked by counsel for Teva if there was any reason why BMS Company could not have required the inventors to assign their priority rights directly to BMS Company, the following exchange occurred between Mr Golian and counsel for Teva:

Mr Golian:	*I don't know. I think the normal practice was to keep intellectual property in the name of the newly acquired subsidiary, and that's what was done here, as reflected in my witness statement and the e mails accompanying that witness statement.*
Counsel:	*So, this was a deliberate step to assign all rights which the inventors had to BMS Pharma?...*
Mr Golian:	[I]*n this instance it was, correct, an assignment of what the inventors had to BMS Pharma.*

v. Name-Change and Inventor Assignment

211. Counsel for Teva read to Mr Golian the section of his witness statement where he states as follows:

"*The same policy described in that e mail* [the 24th October e mail]*...whereby legal ownership of Bristol Myers Squibb Pharma Company's pharma IP assets remained with that entity, and only required a name change from DuPont Pharmaceuticals Company to Bristol Myers Squibb Pharma Company, was in place when I joined BMS Co on 1 July 2002. I was aware of that policy and recall being involved in the preparation and filing of paperwork to effect such name changes around the time I began in BMS Co. Effecting name changes was less costly and time consuming than it would have been to have Bristol Myers Squibb Pharma Company assign all those rights to BMS Co, so there were practical benefits to that approach in circumstances where in my experience and as appears from the October 2001 emails BMS Co in any event had control over the ownership of those intellectual property assets such that it could have decided to have Bristol Myers Squibb Pharma Company assign those intellectual property assets to it at a later date as and when required.*"

212. Asked if this remained his evidence, Mr Golian indicated that it did. The following exchange than occurred between counsel for Teva and Mr Golian:

Counsel:	[T]*he name change was effected on 1st October 2001, isn't that right..?*
Mr Golian:	*It is.*
Counsel:	*And at that time… the priority rights were vested in the inventors?*
Mr Golian:	*I believe that that was in the pleadings, so, yes.*
Counsel:	*So, in the case of US 165, focusing on that particular application, a further assignment was necessary, regardless of the name change, isn't that right?...*
Mr Golian:	*I don't know what you mean by a further assignment was necessary.*
Counsel:	...[I]*n order to transfer the priority rights that the inventors had, an assignment was necessary to a BMS entity, subsequent to 1st October 2001; do you agree with that?*
Mr Golian:	*I think what we have in November 3, 2001…is an assignment of the inventors and the rights that they had to BMS Pharma. And as I mentioned a moment ago, what happened next was the PCT application was filed. And obviously that was in the name of BMS Co, not BMS Pharma one of the reasons I think I'm here today. But when you ask whether another assignment was necessary, I think you may be referring to something that occurred later in 2007….*
Counsel:	*Mr. Golian, I believe you have misunderstood my question….*[A]*t some point after 1st October, an assignment was necessary to transfer the inventors' rights to a BMS entity. Do you agree with that? And I'm not talking about the 2007 Assignment….*
Mr Golian:	*...So, I think in the normal course of our practice, we want to have a written assignment from inventors to someone, and in this case we have the November 3, 2001 assignment from inventors to BMS Pharma….There were previous employment agreements in place and the decision was made to have the inventors assign to BMS Pharma instead of BMS Co, or some other corporate entity.*
Counsel:	*And do you know why that decision was taken?*
Mr Golian:	*I do not.*

vi. Potential Simplicity of Assignment to BMS Company

213. Asked by counsel for Teva whether if the priority rights in US165 had been assigned to BMS Company, rather than BMS Pharma on 3rd November 2001 "*that would have been very simple, wouldn't it?*", the following exchange occurred between counsel and Mr Golian:

Mr Golian:	*I don't know what you mean by 'simple'. If you mean preparing a document and, as shown here, November 3, 2001 but having BMS Co instead of BMS Pharma, I would say yes, you could alter the document accordingly.*
Counsel:	...[I]*t would not have been any more costly or time consuming; can we agree with that?*
Mr Golian:	*So, I think you're referencing paragraph 12 of my witness statement….And what I'm talking about in paragraph 12 is the change of name that occurred from DuPont Pharmaceuticals Company to BMS Pharma and that when I joined in 2002, this was a decision that had been made and it is simpler in the sense of you have a change of name from one entity to another, DuPont Pharma to what became BMS Pharma, which is indeed simpler, to use your word, to use mine, less costly and time consuming than having BMS Pharma assign to BMS Company.*
Counsel:	*But in this particular case, an assignment was required anyway, wasn't it?*
Mr Golain:	*So, if we're focusing on the US 165, as is the normal practice, we have the inventors assigning the rights that they have, in this case, to BMS Pharma.*

vii. The 2007 Assignment

214. Asked why he did not refer to the 2007 Assignment in his witness statement, Mr Golian responded as follows:

> "*I didn't find that this 2007 Assignment was relevant to the points that I wanted to make in my witness statement….* [I]*f we refer to my witness statement…I'm talking about being employed at BMS in 2002, being familiar with the acquisition of DuPont Pharma by BMS and understanding how BMS Company controlled the patent assets of what became BMS Pharma. So, the thrust of my witness statement … was focusing on the policies and procedures of BMS Company managing the patent assets of BMS Pharma.*"

215. Asked, as a Delaware attorney, what he perceived the effects of the 2007 Assignment to be, Mr Golian indicated as follows:

> "[T]*he assignment of April 23, 2007 is from BMS Pharma to BMS.... And in this assignment, BMS Pharma is granting to BMS Co whatever rights it may have with respect to US 165 and all patent applications, patents relating thereto. This is again, I think, another form* [of?] *assignment where it says things like the entire right, title and interest in all countries of the world, but it doesn't necessarily mean that BMS Pharma is granting to BMS Co all of those rights; it may be something that BMS Co already has. I would also say that these sorts of assignments are often used to be recorded with Patent Offices to basically have a legal document reflecting, to the extent there's any ambiguity, BMS Pharma is granting to BMS Co various rights*."

216. Mr Golian was referred by counsel for Teva to his evidence in Finland where Mr Golian stated, "*I would describe this assignment as a belt and suspenders approach. And what I mean by that is,*

to the extent that there were any residual rights, this assignment from BMS Pharma to BMS Company would address those residual rights." Asked if he agreed with that statement Mr Golian said that he agreed with this statement.

217. Turning to the actual wording of the assignment and, in particular, the first clause of the operative language ("*…does hereby assign to a assignee the entire right, title and interest…*") Mr Golian was asked to confirm that that language connotes beneficial, equitable and legal interests in the asset. At this point the following exchange occurred:

Mr Golian:	*I think that these are phrases that are used in a template assignment agreement that covers everything under the sun, but it doesn't necessarily reflect the rights that the assignor, in this case BMS Pharma, has at this time.*
Judge:	*But I think everybody agrees you can only assign what you can assign. I think what counsel is really getting at is what exactly did you assign? …*
Mr Golian:	[Short pause] *So, I would say this is a document that would be useful to show the legal title is in the name of BMS Company rather than BMS Pharma Company*.
Counsel:	*And again, can you direct the Court to where there's a reference to legal title in this document?*
Mr Golian:	*It's not in this document….*[T]*his would be an assignment, in 2007, to show, at least in a paper document, you don't necessarily need paper documents to have an assignment of rights, it can happen in other ways but this is a document that would be used with Patent Offices.*
Judge:	*Well, I assume one of the arguments I'm going to get at the end of the day is that words have meaning. So, you're saying these words don't mean what they say, is that it?*
Mr Golian:	*I think that this is a document with words that have meaning, but it has to be in the context of the rights that one has or doesn't have.*

218. Asked by counsel to "*compare the phrase 'the entire right, right, title and interest in', which relates to US 165 itself, and contrast that with the language used in the same assignment "any remaining right, title and interest in all countries of the world in and to any patent application claiming priority from US 165*", Mr Golian was then asked was it not open to Mr Bonk, or whoever drafted the assignment, to simply replicate that language in the first clause of the agreement, if what was intended was to simply assign what BMS Pharma then had. To this, Mr Golian responded that he did not know why the language was drafted as it was.

viii. Role of BMS Staff in Subsidiaries

219. Turning to the role of BMS staff in BMS subsidiaries, the following exchange occurred between Mr Golian and counsel for Teva:

Mr Golian:	*I don't know how having officers and directors of BMS Pharma such as Sandra Leung or David Bonk or Nadine Flynn would have been relevant to what I put forward in my witness statement.*
Counsel:	[P]*erhaps I should explain why I think it is relevant….Mr. Howard asked you about the personnel involved in different matters affecting BMS Pharma's IP and you indicated BMS Pharma did not have its own employees…*[a]*nd in your witness statement… you say:*

'From the commencement of employment with BMS on 1 July 2002, my experience has been that decisions as to how intellectual property assets are to be held have been made by BMS Co for both it and its wholly owned subsidiaries. Typically, these decisions are made by BMS Co's intellectual property lawyers, often in consultation with BMS Co's tax department and other areas of BMS Co's Legal Department'….

Counsel: *So, the fact that the people you go on to name also had roles in BMS subsidiaries, important roles as directors and officers of those subsidiaries is surely relevant to that evidence, is it not?*

Mr Golian: *I think me learning just now that individuals such as Sandra Leung, David Bonk and Nadine Flynn also had responsibilities as directors or officers of BMS subsidiaries doesn't change the evidence that I've provided in my witness statement.*

ix. The 2016 Assignment

220. Counsel turned next to the 2016 assignment and asked Mr Golian for his view as to the effect of same. To this, Mr Golian responded as follows:

"[T]*his is an assignment from BMS Pharma to BMS Company…. a confirmatory assignment…. 'I think the purpose of this document in 2016 is, I want to make it clear to the world so that there's no doubt whatsoever, I'm going to name the patent applications and patents; these rights might have already been transferred and I want in this document to make it crystal clear that BMS Company owns these US patents in Exhibit A.'*"

221. Turning next to a draft of the 2016 assignment, counsel for Teva referred Mr Golian to an annotation on that draft text which has been inserted at the point of the sentence "*Assignor covenants that Assignor had or has the right to enter into this Patent Assignment*". This annotation reads: "*Otherwise, BMS Pharma Co is covenanting that they still own the patents even after the 2007 Assignment right? Or is it fine as is because they still have the right to confirm what they've already done?*" Counsel then put it to Mr Golian that the natural inference from that comment is that BMS Pharma owned application '165 up to the date of the 2007 Assignment. To this, Mr Golian responded as follows: "*I have no idea who's making this comment and no context for what they know or don't know.*"

222. When it comes to the 2016 Assignment, Teva submits as follows in its written closing submissions:

"*2.24* *For reasons unknown to Teva, BMS Pharma executed <u>another</u> assignment of US165 and its priority rights, on 13 November 2016 (the "2016 Assignment"). Again, extraordinarily, this is not acknowledged in the statements of Ms Leung, Mr Golian and Ms Mathias.*

2.25 *The careful drafting of the 2016 Assignment bears emphasis. On its face, it acknowledged the earlier assignment by BMS Pharma ('Assignor hereby confirms that (i) it previously sold, assigned' etc.) and its operative clause is confined to residual rights held by the assignor, BMS Pharma ('to the extent, if any, that Assignor has not done so, Assignor hereby sells, assigns…' etc.).*

2.26 *The contrast between the 2007 and 2016 Assignments is patent. As neatly stated by Ms Leung, 'one is confirmatory and one is not.' Nonetheless BMS' witnesses adhere to the position that <u>both</u> were 'belt and suspenders' assignments.*

2.27 *This was clearly not the understanding of BMS at the time of drafting the 2016 Assignment. A mark-up of the 'Covenant' remarks that, without a proposed change, "BMS Pharma is covenanting that they still owned the patents even after the 2007 Assignment right?" The clear (and correct) inference was that BMS Pharma <u>did</u> own US165 before the 2007 Assignment.*"

223. Four points might be made.

224. First, as to §2.24, the degree of extraordinariness presenting is directly proportional to the importance of the 2016 Assignment to the case at hand. As I have previously stated, Teva has sought to make great play of the 2007 and 2016 assignments in this case, suggesting that the rationale for same has never been explained by BMS (not that a duty of explanation arises). However, to examine the 2007 and 2016 assignments (and the efforts to parse them) is a distraction. This is because, as a result of the Common Delaware Evidence, the most that can have been transferred in the assignments of 2007 and 2016 was BMS Pharma's legal interest. Thus, it seems to me to get one nowhere in the circumstances presenting to consider the wording of the assignments of 2007 and 2016 in any detail. As extraordinariness is, in the present context, directly commensurate to relevance, and as the 2007 and 2016 assignments, for the reasons stated, have no especial significance, it follows that no extraordinariness presents.

225. Second, as to §2.25, I do not know how carefully the 2016 Assignment was drafted (and, with respect, neither does Teva). What I do know is that efforts to parse the assignment are a distraction for the reasons stated in the preceding paragraph.

226. Third, as to §2.26, if one looks to the full paragraph in which the snippet quoted by Teva appears, Ms Leung is making a very different point to what one might imagine, observing as follows:

> "*The 2007 Assignment was done, as I understand it, perhaps in a different context. And so I don't infer anything into, I don't read anything into the fact that one is confirmatory and one is not, because the underlying facts are BMS Company controlled completely the IP assets that were formerly owned by the former DuPont company.*"

227. In other words she is stating that the purpose of the 2007 assignment does not matter, *i.e.* she is stating the very opposite of what Teva contends for in §2.26. And, again, I would respectfully make the point that to examine the 2007 and 2016 assignments (and the efforts to parse them) is a distraction for the reasons stated above. I do not see that "*BMS' witnesses adhere to the position that <u>both</u> were "belt and suspenders" assignments.*" They simply state that this is so and given that they perceive this to be the truth, there is no reason for them to depart from that truth.

228. Fourth, as to §2.27, I admit to some surprise that Teva would seek to place any reliance on an anonymous note scribbled on a document. It is not known who wrote it and all of us as lawyers when we review a document scribble comments as we go along, some good, some bad, some that we may abandon when we talk to someone or have an email exchange in relation to the matter. Sometimes we scribble thoughts and never actually return to them again. The notion that there is some legal significance to someone's anonymous scribble is, with respect, a notably weak line of contention.

x. Emails of October 2001

229. Counsel for Teva referred next to the email of 19th October 2001 and summarised some of Mr Golian's averments in his statement namely "*that BMS Company has always made the decisions as to how it and its wholly owned subsidiaries hold their intellectual property assets and that that is*

borne out by this email". Counsel then put it to Mr Golian "*that this email simply records that the IP is held by BMS Pharma.*" To this, Mr Golian responded that "*while the email itself doesn't say BMS Co, it's talking about what are now wholly owned subsidiaries of BMS Co. And these are BMS Co employees talking about these subsidiaries…. I don't think they're making decisions, I think they are sharing information.*"

230. Counsel for Teva next noted that in his witness statement, Mr Golian states as follows:

> "*The 24 October 2001 e mail reflects decision making by BMS Co as to the legal ownership of Bristol Myers Squibb Pharma Company's intellectual property, and the putting in place of a policy in that regard, consistent with my experience of BMS Co being the decision maker and having control over how the intellectual property assets of its wholly owned subsidiaries are to be held*",
>
> and asked if that remained his evidence. Mr Golian indicated that it did.

231. Counsel for Teva turned next to the email of 24th October 2001, of which Mr Golian stated that "[T]*his is evidence of BMS Co controlling the patent assets of BMS Pharma and BMS Co making decisions with respect to the patent assets of BMS Pharma.*" Asked to comment on the substance of these decisions, Mr Golian indicated as follows:

> "[T]*here's a discussion with respect to legal ownership. And again, in paragraph 1, maintain legal ownership in BMS Pharma and the new patents and trademarks. So, I take this to mean new patent and trademarks coming from what is now BMS Pharma in Wilmington, Delaware, that the new patents and trademarks would be in the name of BMS Company.*"

232. Asked by counsel for Teva to comment on what he understands the email to mean when it refers "*maintain legal ownership*", Mr Golian indicated that "[T]*his is a BMS Co tax individual commenting and she uses the phrase "legal ownership" which I suspect is legal title.*"

233. Asked by counsel for Teva if the email reflected policy, and if the policy had been followed in this case, in terms of how the Patent Cooperation Treaty application would have been filed, Mr Golian indicated as follows:

> "[I]*f I'm looking just at the 24 October 2001 e mail, we have two categories of patents; we have those that occurred prior to the acquisition in October 2001 and the guidance reflected in here is the decision made is to maintain those in BMS Pharma. And then we have the second category with respect to new patents. And with respect to new patents, so presumably a priority application after October 2001, that those would be in the name of BMS Company. What we don't have here, in this 24 October 2001 email, is a third category where the priority application is filed before October 2001 and the PCT application is filed afterwards. So, I would say this October 24, 2001 email does not address that third category.*"

234. Asked by counsel for Teva whether the policy set out in the email was implemented by BMS, Mr Golian indicated as follows:

> "*I would say this is a decision that is being discussed here within the BMS Company Tax and BMS Legal Group. But it's one of many things. The policy was the practice of BMS Co controlling and managing the patent portfolio of BMS Pharma, and this 24 October 2001 email is just one of many things that are occurring to establish, as I've said in my witness statement, the policy of BMS Co controlling the patent portfolio of BMS Pharma.*"

235. Counsel for Teva asked Mr Golian whether the BMS policy was the substantive decision reflected in the email. To this, Mr Golian indicated as follows:

> "[T]*he policy is how BMS Co. operated with respect to managing and controlling the BMS Pharma portfolio. So, this e mail is just that, it's one e mail. And it's establishing individuals within BMS Co's Law Department, BMS Co's Tax Group making decisions with respect to legal ownership of the BMS Pharma patents. What we don't have here is BMS Pharma having its own law department or BMS Pharma having its own tax group or other advisers, we have BMS Co individuals making decisions with respect to the BMS Pharma patents. And again, this e mail is focusing on the decisions with respect to legal ownership.*"

236. Counsel asked next whether the policy was that BMS Company would control its subsidiaries Mr Golian indicated that this was so.

xi. Distinction between Right of Control and Policy on Holding of Patents?

237. Counsel for Teva noted that in one its replies to particulars, BMS has stated as follows:

> "*As already particularised the right of control of Bristol Myers Squibb Company over intellectual property of Bristol Myers Squibb Pharma Company arose under Delaware law as a result of its acquisition of 100% ownership in that entity. As indicated, upon acquisition, Bristol Myers Squibb Company exerted its right of control by laying out the policy as to how patents were to be held as between the companies such that ownership of existing patent and trademark rights related to the pharmaceutical business of Bristol Myers Squibb Pharma Company should remain in that company.*"

238. Counsel then put it to Mr Golian "*that that pleading draws a distinction between a right of control on the part of BMS Company and the policy as to how patents were to be held as between the companies.*" To this, Mr Golian responded as follows:

> "*I think that the policy is simply stated as BMS Co controlling all of the decision making with respect to the BMS Pharma patent portfolio, it's as simple as that….*[O]*ne component of that policy is BMS Co making the decision to have the existing BMS Pharma patent portfolio remain with BMS Pharma.*"

239. Counsel for Teva put it to Mr Golian that there is a distinction between (i) asserting a right of control and (ii) exercising that right of control by laying out the policy as to how intellectual property assets were to be held between the different entities. The following exchange then ensued between Mr Golian and counsel for Teva:

Mr Golian:	*…I would say "the policy" entails more than just ownership, it entails, again, all aspects of patent filings, patent litigation, patent licensing etc. So, it was BMS Company that had a policy by how it operated of controlling and managing, including but not limited to ownership of the BMS Pharma patent portfolio.*
Counsel:	*So, is it your evidence then that BMS Company's policy was to control everything?*
Mr Golian:	*It was BMS Company's policy to have control of, and to manage, the BMS Pharma patent portfolio, yes.*

xii. The Email of 30th January 2002
(The Blair Ferguson Email)
[The text of this email is in chapter 2]

240. Asked about the Blair Ferguson email of 30th January 2002, the following exchange (focused on the distinction between guidance and policy) occurred between Mr Golian and counsel for Teva:

Mr Golian:	*...I think this e mail from Blair Ferguson dated January 30, 2002 is, as mentioned in the email, is a guideline that should be followed. And this email is addressing that third category of patent filings ... it's saying if the provisional's filed prior to October 1, 2001, all subsequent filings worldwide claiming this priority should be in the name of BMS Pharma. So, this is guidance by Blair Ferguson, a patent attorney at BMS Co, with respect to filing patent applications in the name of BMS Pharma versus BMS Co.*
Counsel:	*You used the term 'guidance' a number of times in your answer. Are you intending to draw a distinction between guidance and a policy?*
Mr Golian:	*I am.*
Counsel:	*What is that difference?*
Mr Golian:	*I think that guidance is reflected here. And as I said a moment ago, there's guidance to follow what's specified in this e mail. But the underlying policy, as we've discussed, is how BMS Co. operated and how BMS Co was responsible for managing and making decisions with respect to the BMS Pharma portfolio….So I want to try to explain, there are all sorts of aspects of buying up a big company and integrating that company. It often takes years. There's lots of decisions that need to be made. And this guidance here in this Blair Ferguson email is just one aspect of this practice that we had of BMS Company making decisions and managing this BMS Pharma portfolio.*

241. Asked by counsel for Teva if Mr Ferguson was the chief patent counsel for BMS Co., Mr Golian indicated that he was not.

242. Asked by counsel for Teva "[w]*hat harm is Mr. Ferguson anticipating if things are not done the way he tells people that they should be done*", Mr Golian answered as follows:

> "*This email from Blair is to a group of individuals that are patent paralegals and patent attorneys responsible for BMS Pharma patent matters, and he's providing guidance on what to do with this third category of patent filings. He's answering a question that at least some… are asking about this category of patent filings.*"

243. Asked by counsel for Teva whether the purpose of the email was to protect priority rights, Mr Golian responded as follows:

> "*I think that the purpose of this e mail is simply to provide guidance. It includes not only priority rights, which are certainly one consideration, but also there could be other considerations for keeping this third category in the name of BMS Pharma versus the name of BMS Co. And this is yet more evidence of BMS Co making decisions on what to do with BMS Pharma patent filings*."

244. Asked by counsel for Teva about his just-quoted reference to "*other considerations*" and what these might be, Mr Golian responded as follows:

"[W]*e looked* [*i.e.* previously in the course of Mr Golian's testimony] *at emails before where BMS Co lawyers and BMS Co tax advisers were making decisions on those first two categories. So, patent applications that originated at DuPont Pharma would now be in the name of BMS Pharma and anything new -- meaning having a priority after October 1, 2001 … those would be in the name of BMS Co. And I suspect that those sorts of legal and tax considerations are now being applied to this third category and Blair Ferguson is providing guidance based on his…understanding – I don't know who he consulted with – but his guidance with respect to this third bucket of patent filings*".

245. Asked by counsel for Teva whether Mr Ferguson's advice was followed by the person who filed the PCT application, the following exchange occurred between Mr Golian and counsel:

Mr Golian:	*It was not….*
Counsel:	*And had it been followed, would there have been any issue in relation to priority rights from US 165?*
Mr Golian:	*I would say if the guidelines here were filed, we would have US 165 in the name of BMS Pharma….And we would have WO652 in the name of BMS Pharma. And it would be clear from those filings that it's the same entity named for both the priority application and the PCT application.*

xiii. The BMS Manual

246. Asked about the manual and its status (including its usage by BMS attorneys) the following exchange occurred between counsel for Teva and Mr Golian:

Counsel:	*Can I ask you, in general terms, about your own familiarity with the manual during your time at BMS?*
Mr Golian:	*...I was aware that there was a paralegal manual, but it's not something that I used in my work, not something I referred to.*
Counsel:	…[W]*as it the general practice of patent attorneys in the BMS Company Legal Department to refer to this manual?*
Mr Golian:	*No, I think the general practice was patent attorneys were not using this manual….*
Counsel:	*So, how would they inform themselves as to the appropriate entity to put on to a PCT application?*
Mr Golian:	*The patent attorney would know from their training and work experience how to file various documents, including PCT applications….*
Counsel:	[I]*n the specific context of PCT applications filed which claimed priority to DuPont Pharma applications prior to 1st October 2001, how would the patent attorney inform themselves of the appropriate course of action to take?*
Mr Golian:	[W]*e have guidance from Blair Ferguson in an email that we discussed this morning. And that's an example of a discussion within the BMS Company Law Department as to how to file and prosecute patent applications, including the name of the applicant, the name of the assignee that is holding various rights.*
Counsel:	*…And I think we agree, Mr. Golian, that there is no material difference between the relevant part of that e mail and the bold text we're looking at on page 171,* [of the manual] *isn't that right?*
Mr Golian:	*That's right.*

247. Asked by counsel for Teva if the manual and accompanying email was circulated to lawyers and paralegals, Mr Golian indicated that this was so. Asked if the instruction/guidance in the manual would have been necessary if BMS Company already had and enjoyed the right to priority, the following exchange occurred:

Mr Golian:	*I think if there was a decision made I think if BMS Company had the right to claim priority to the US 165, they would be able to do so irrespective of the guidance that's provided in Blair Ferguson's email and Dora Lynch's updating to this manual.*
Judge:	*Is it not more than guidance? There's a provision in there somewhere, isn't there, saying you can't deviate from this practice unless the entire body of attorneys within BMS have agreed to that deviation? ....*
Counsel:	*Yes....*[A]*t the top of page 104 Ms. Lynch states: 'I'm sure we'll have many discussions among the attorneys to evolve this Training Manual into something that is acceptable to all. The point is that the collective attorney group can* [a]*gree to make changes, but no individual attorney can make procedural changes'....*[D]*oes that not mean that the manual is in fact an instruction and not mere guidance?...*
Mr Golian:	*....I think…the idea was, across the Patent Department, to kind of standardise things.*
Judge:	*But not even an attorney is higher than the guidance/instruction, whatever we call it?*
Mr Golian:	*Well, I think that's Dora Lynch's view.*
Counsel:	*Ms Lynch says: 'This Manual will be constantly updated to reflect any changes necessitated by PTO Rule Changes or Internal Department Changes and should be adhered to by all three sites.' Again, is that not consistent with the manual constituting an instruction which is to be adhered to rather than mere guidance?*
Mr Golian:	*I think these are the words that Dora Lynch, who was leading the patent paralegal group, chose to use….But… ultimately patent attorneys are responsible for their work, and they might choose to deviate from this instruction, this guideline, rightly or wrongly….*
Counsel:	[D]*oes it say anywhere in the manual or in this email that individual attorneys can depart from the guidance or instructions in the manual?*
Mr Golian:	*I'm certain it probably doesn't say that anywhere.*

xiv. Consequences of Compliance with BMS Manual

248. Counsel for Teva returned to the issue of what the practical implications of compliance with the manual would have been, stating, "*I'll use the term 'guidance', but it shouldn't be taken as my agreement that that's what this is, but just not to trip us up if this guidance were followed in relation to the patent in suit, who would've been the applicant for the patent?*" To this, Mr Golian responded that "*If this guidance on page 171 had been followed, the priority US 165 would've been in the name of BMS Pharma*".

249. Counsel posited that "[I]*f the guidance had been followed, there would be no need to rely on equitable interest or equitable title or beneficial title*". Mr Golian agreed that this was so. Counsel for Teva later returned again to this point asking: "[I]*sn't it the case that, as with the application you filed in the name of BMS Pharma… there would be no need to rely on alleged equitable title to establish a chain of priority in relation to this patent?*" Mr Golian again indicated that this was so.

250. Counsel for Teva brought Mr Golian to a summary table prepared by Teva's solicitors showing various (43) PCT applications and whether or not they were effected in accordance with the manual. At this juncture the following exchange occurred between counsel and Mr Golian:

Counsel:	[M]*y solicitors have prepared a table which summarises .... 43 PCT applications*....[a]*nd the ones identified in pink are all in the name of BMS Pharma; the ones in yellow are in the name of BMS Company; there are two in the name of BMS Company Patent Department; and one is in the name of BMS Medical Managing Inc*.... [I]*f you just take it that that is the position, Mr. Golian, can I ask you to agree with me that that sometimes the guidance in the manual was implemented?*
Mr Golian:	*Yes, I agree*....
Counsel:	*And sometimes…was not.*
Mr Golian:	*Yes, I agree.*
Counsel:	*And do you agree with me that there was, therefore, an inconsistent approach to PCT applications claiming priority in the year following the acquisition of DuPont?*
Mr Golian:	*I would say that …the guidelines, the guidance was not always followed. I had a chance, because I had a little time, to review the tab 3 PCT applications. There were 38 of them. And I didn't get a chance to review the index which has 43… [because it] was Monday night. But with respect to tab 3, as I mentioned, there are 38 PCTs. And by my count, 20 of them followed the guidance in the Blair Ferguson e mail and the paralegal manual, which leaves 18 that did not. And for the 18 that did not follow the guidance, there were three practitioners that did not follow the guidance. So, three practitioners. Whereas with respect to the 20 that did follow the guidance, that included nine different patent attorneys. So, in preparing for my evidence today, I just found it notable that there were three people that seemed to not follow the guidance, although even those that didn't follow the guidance, they sometimes did*….
Judge:	*I assume their defence will be it was guidance, not an instruction* [?]....
Mr Golian:	*I think it reflects what we have at this time; we have DuPont Pharma being acquired by BMS, lots of people leaving the organisation, a very significant integration, as we've discussed this morning, a large patent portfolio. And it's the patent attorney's job to get this right, this is important. But somehow, between the paralegal and the patent attorney, it wasn't always done the way the guidance said to do it. It's probably people using templates that say BMS Co were working in some sort of software generating thing that says BMS Co. And again, 20 times the guidance was followed, 18 it wasn't. Was it a mistake? I can only speculate.*
Counsel:	*So, you really don't know why that happened, isn't that right?*
Mr Golian:	*That's right.*

xv. Previous Reliance on Equitable Ownership?

251. Counsel next turned to the question of whether, apart from the present proceedings, BMS has relied on equitable ownership in the context of asserting priority or obtained legal advice in this regard, the following exchange unfolding between counsel and Mr Golian:

Counsel: [A]*part from this patent application, are you aware of any other scenario where BMS has relied on beneficial or equitable ownership to found a claim of priority?*

Mr Golian: *I'm not.*

Counsel: *And did you or your colleagues in the BMS legal team ever obtain any analysis of equitable ownership as a basis for claiming priority?*

Mr Golian: *To my knowledge, outside of this case, no.*

xvi. Opinion of Morris, Nichols, Arsht and Tunnell, and Dual Roles of Dr Larsen

252. Counsel for Teva turned to a legal opinion issued by Morris, Nichols, Arsht and Tunnell in the context of opposition proceedings before the EPO. That opinion amongst other matters, states as follows:

"*We have been requested to provide advice on the issue whether under Delaware law BMS Pharma constitutes a successor in interest to the pharmaceutical business previously conducted by The DuPont Merck Pharmaceutical Company ('DuPont Merck Pharma'). As more fully set forth in our numbered opinion paragraphs below, and for the reasons and based on the events recited therein, it is our opinion that BMS Pharma is a successor in interest to the business of DuPont Merck Pharma.*"

253. Counsel for Teva noted that the relevant period for the purposes of the opinion extended from 1998 through to 10 September 2002 and thus (and was confirmed by Ms Golian) includes the priority year as regards the patent in issue in these proceedings. Counsel then noted the section of the opinion that states as follows:

"*Section 2.6 of the Partnership Agreement provides that all assets and properties owned by the Partnership shall be held and recorded in the name of the Partnership and shall be deemed to be owned by the Partnership*",

at which point the following exchange took place between counsel and Mr Golian:

Counsel: *Have you consulted the Partnership Agreement of BMS Pharma for the purpose of giving your evidence in these proceedings?*

Mr Golian: *I have not…*

Counsel: [I]*f it* [the text of opinion] *is an accurate representation of the Partnership Agreement, doesn't it appear to be clear that the terms of that agreement deem all assets to be owned by the partnership?*

Mr Golian: *So, I'm looking back on the first page… and the partnership is referring to Dupont Merck. And coming to your question… in this paragraph 2 it's talking about Section 2.6 in this paragraph 2 it's talking about Section 2.6 of the Partnership Agreement provides that all assets and properties owned by the partnership shall be held and recorded in the name of the partnership. So, just reading this now, it seems that this paragraph 2 is talking about what was once known as DuPont Merck, DuPont Merck Pharma.*

Counsel: *And is it your understanding that the Partnership Agreement remains in effect as the Partnership Agreement of BMS Pharma?*

Mr Golian: *I don't have knowledge on how this worked.*

254. Counsel for Teva turned next to the section of the opinion that reads as follows:

"*Pursuant to the BMS Purchase Agreement and the BMS Acceptances, on October 1, 2001 DuPont and DPI respectively conveyed their partnership interests in the*

Partnership (constituting collectively all of the partnership interests in the Partnership) to E.R. Squibb and BMS Pharma, respectively, and E.R. Squibb and BMS Pharma were admitted as general partners of the partnership in substitution for DuPont and DPI. The business of the partnership was continued by E.R. Squibb and BMS Pharma pursuant to Section 6.1 of the Partnership Agreement and applicable Delaware law",

and an associated footnote which states as follows:

"*Pursuant to the Instrument of Acceptance forming a part of the BMS Acceptances, E.R. Squibb and BMS Pharma acknowledge (i) their respective purchases of the DPC Interests... (ii) their admission as general partners... and (iii) their agreement to be bound by the provisions of the Partnership Agreement,*"

with the following related exchange ensuing between counsel for Teva and Mr Golian:

Counsel: …[B]*ased on that, could I ask you to indicate whether you agree that the Partnership Agreement continued to bind BMS Pharma as of September 2002?*

Mr Golian: …[T]*he opinion of this law firm in paragraph 8...*[is that] *for these reasons, the business of DuPont Merck Pharma has been continued by, and is vested in, BMS Pharma and BMS Pharma constitutes a successor in interest to the business of DuPont Merck Pharma. I see that.*

Counsel: *Yes. And paragraph 7, would you read that out, Mr. Golian?*

Mr Golian: *Yes. In paragraph 7:*

> *'As of the date hereof, BMS Pharma continues its existence as a general partnership in good standing under the laws of the State of...*[Delaware], *conducting business under the name Bristol Myers Squibb Pharma Company.'*

Counsel: *Thank you. And can I just ask you to agree with me that this Partnership Agreement, as it's described in this opinion, is inconsistent with partners or their parents asserting beneficial interests in the assets owned by BMS Pharma?*

Mr Golian: *I don't know what this relates to.*

255. The opinion makes reference to an affidavit by Dr Larsen, who describes himself in that affidavit as patent counsel at BMS Company and BMS Pharma. In this regard, the following exchange occurred between counsel for Teva and Mr Golian:

Counsel: [C]*an you explain to the Court why Dr. Larsen would have dual roles in the two entities?...*

Mr Golian: *The role of a patent attorney was to manage and direct the patent portfolio of BMS Company, which included managing all patent matters on behalf of BMS Pharma. So I take, this …to mean Scott Larsen is a BMS Company patent attorney, also having responsibility for, in this case … relating to an Amersham patent that is currently in the name of BMS Pharma and he's establishing how BMS Pharma ties back originally to DuPont Merck Pharmaceutical… trying to connect the dots for the EPO that he has this dual responsibility….*

Counsel: [C]*an I ask you to confirm that in your witness statement you identify BMS attorneys and paralegals and so on as having roles only in BMS Company…?*

Mr Golian: *The way I said it was that BMS Pharma didn't have its own employees, rather it was the Law Department of BMS Company that was managing the patent assets of BMS Pharma. And Mr. Larsen was one of many of the BMS Co Legal Department that was responsible for managing the patents and patent counselling relating to BMS Pharma.*

256. Counsel for Teva drew the attention of Mr Golian to the following averment of Dr Larsen

> "*THE DUPONT MERCK PHARMACEUTICAL COMPANY, its successor in business assets, DUPONT PHARMACEUTICALS COMPANY, and its successor in business assets, BRISTOL MYERS SQUIBB PHARMA COMPANY have continuously, without interruption, been in the business of research, development, registration, manufacture, distribution, marketing, and sale of human pharmaceutical products, including, but not limited to, radiopharmaceutical products since 1995. That, BRISTOL MYERS SQUIBB PHARMA COMPANY, as successor to DUPONT PHARMACEUTICALS COMPANY, carried on the business previously conducted by DUPONT PHARMACEUTICALS COMPANY; and that DUPONT PHARMACEUTICALS COMPANY, as successor to THE DUPONT MERCK PHARMACEUTICAL COMPANY carried on the business previously conducted by THE DUPONT MERCK PHARMACEUTICAL COMPANY*."

257. Having drawn Mr Golian's attention to the foregoing, the following exchange then occurred between counsel and Mr Golian:

Counsel: *The successor in business assets is identified as BMS Pharma, isn't that right?*

Mr Golian: *Yes. But as I said, this is in the context of an affidavit by Mr. Larsen to the European Patent Office. So, when we talk about successor in business assets, I read this as for purposes of what the European Patent Office is concerned with. I think successor in business assets can mean different things in different contexts, that's the point I'm trying to make…*

Counsel *[C]an you confirm that he identifies the successor in business assets as being BMS Pharma Company and not BMS Company?*

Mr Golian ....[A]*s I said, it's in relation to whatever this matter is with the EPO. It may be not for things different from the EPO, I just don't know.*

258. Counsel for Teva queried whether when it came to the phrase "*business assets*" in the above quoted averment of Dr Larsen, Mr Golian was reading that phrase as being confined to agreements with third parties. At this juncture the following exchange occurred between counsel for Teva and Mr Golian:

Counsel: *Are you reading the term "business assets" as being confined to agreements with third parties?*

Mr Golian: *I'm not.*

Counsel: ...[I]*sn't it true that a patent application for a pharmaceutical company is a business asset?*

Mr Golian: *I think that a patent application would fall under what business assets are, yes….*

Counsel: *....Do you have any reason to doubt the accuracy of what's set out in paragraph 8* [of Dr Larsen's affidavit]*?*
Mr Golian: *I don't.*

259. Counsel for Teva turned to the decision of the EPO in which the above- mentioned opinion of Morris, Nichols, Arsht and Tunnell featured. She asked Mr Golian whether he agreed with the following conclusion of the EPO Board of Appeal:

> "*It follows that the appellant partnership which, as 'any person' (see Article 99 EPC), filed opposition to the patent in suit, was also 'a person aggrieved' (see Article 107 EPC) by the decision under appeal and therefore entitled to commence and prosecute the present appeal proceedings.Since, on the only evidence available to the Board, the appellant has throughout remained the same entity, no question arises of any transfer to another party of the appellant's assets or of its status as opponent or appellant*",

which question led to the following exchange between Mr Golian and counsel for Teva:

Mr Golian: *I'm not an expert on European patent law, but I think within the confines of the Larsen affidavit and this decision, it makes sense that BMS Pharma had the right to continue the opposition that was started by what was originally DuPont or DuPont Merck.*
Counsel: *The Board of Appeal, in that sentence that we've just discussed, uses the term "assets". And you'll agree with me, I presume, Mr. Golian, given your earlier evidence, that an application for a patent is, from the perspective of a pharmaceutical company, an asset of that company?...*
Mr Golian: *I think a patent application is an example of a business asset, yes.*
Counsel: *Are you drawing a distinction between business asset and asset?*
Mr Golian: *I'm sorry, asset. I was referring to the phrase that was used before. But for this discussion, asset, yes, a patent application is an asset.*

260. Asked by counsel for Teva to confirm that the phrase "*business assets*", as used by Dr Larsen was not limited to radiopharmaceutical assets, Mr Golian indicated that this was so.

261. Counsel for Teva drew Mr Golian's attention to the last portion of the above-quoted averment of Dr Larsen, which stated that that the Partnership Agreement of 31 October 1995 '*remains in effect as the partnership agreement of BRISTOL MYERS SQUIBB PHARMA COMPANY; and that no event or occurrence that would cause a dissolution of the partnership under Section 7.6(a) of the Partnership Agreement has occurred*', and asked Mr Golian "*to agree with me, certainly at this point in time the Partnership Agreement recorded in the opinion of the law firm remains in effect*". To this, Mr Golian responded that "*That's the opinion of the law firm and the opinion of Mr. Larsen...I see that.*"

xvii. Why Mr Golian was Proffered as a Witness

262. Turning next to why Mr Golian had been proffered as a witness in these proceedings, the following exchange occurred between counsel for Teva and Mr Golian:

Counsel: *Mr. Golian, you weren't involved in the 2007 Assignment or any of the 2001 or first half of the year 2002 e mails or the manual, isn't that right?*
Mr Golian: *Correct.*
Counsel: *And I don't mean this in any way disrespectfully, I just want to ask you, given your lack of involvement in relation to those matters, do*

	you know why you were asked to give evidence in these proceedings?
Mr Golian:	*I think in forming my witness statement, I was familiar with a number of the individuals on the e mails that were included as exhibits and I was able to talk about joining BMS in 2002 and what I experienced and that I had in fact filed a patent application that had a priority filing before October 2001 and a 12 month filing after. This is obviously 20/21 years ago, so maybe I was the only person available. But I don't know why I was chosen, I just know I had something to offer, and that's what I've provided in my witness statement as well as the evidence today.*

xviii. Patent Cooperation Treaty Application Filed in Name of BMS Pharma

263. By way of closing question, counsel for Teva put it to Mr Golian that "[U]*ntil today, Mr. Golian, in any of your witness statements or testimony, you've never referred to the PCT application which you filed in the name of BMS Pharma, isn't that right?*" Mr Golian confirmed that this was so.

D. Re- Examination

1. Legal Opinion and Dr Larsen

264. Counsel for BMS asked Mr Golian to confirm that nowhere in the legal opinion of Morris, Nichols, Arsht and Tunnell or in the associated affidavit filed by Dr Larsen is there a listing or identification of any patents that were, at that time, in the name of BMS Pharma, Mr Golian confirmed that this was so.

2. Successor in Interest versus Beneficial Ownership in Patent

265. Counsel for BMS asked Mr Golian to confirm that when Dr Larsen's affidavit "*is addressing successor in interests to a business… that* [is] *a different enquiry to determining whether or not one entity would have beneficial ownership in a patent in the name of another*". To this, Mr Golian responded that "*I think successor and interest in beneficial ownership can be different things.*"

3. Role of BMS Employees

266. Turning to the issue of who employed Dr Larsen and others, the following exchange occurred between counsel for BMS and Mr Golian:

Counsel:	*As of September 2002, who do you recall employed Mr. Scott Larsen as an employee?*
Mr Golian:	*BMS Co.*
Counsel:	*And insofar as it was put to you that there were people …. in executive officer or director positions post 1st October 2001… think this was end 2002 who was the employer of those people that were identified?*
Mr Golian:	*BMS Co.*

4. The EPO judgment

267. Turning to the substance of the EPO Proceedings to which counsel for Teva had brought Mr Golian, the following exchange occurred between counsel for BMS and Mr Golian:

Counsel: [As] *to the issue that the EPO appeared to be enquiring into in this judgment….*[t]*he enquiry here appears to be whether the party opposing a patent of another party met the requirement of being adversely affected by that filing, is that correct?*

Mr Golian: *Yes.*

Counsel: *There was no enquiry here in respect of the validity or ownership of any patent of BMS, isn't that correct?*

Mr Golian: *That's correct.*

Counsel: *Then if you go forward to the next page…there's a summary here in relation to the nature of the argumentation engaged in by the respondent patentee. And it makes the argument here, if you look towards the bottom of page 34* [p10 of judgment]: *'"The business formerly conducted by the appellant partnership was now being conducted by that corporation, which was therefore the successor in business to the partnership.'" That's the nature of the enquiry, isn't that correct?*

Mr Golian: *....Yes.*

Counsel: *And then when we go to the decision, that you were brought to, on page 44*[p20 of judgment], *that was resolved, as indicated, on the basis that: 'The Board is now satisfied that, under Delaware law, that partnership has, notwithstanding changes of both participating partners and of name, continued in being throughout the appeal proceedings.' Isn't that correct?*

Mr Golian: *Yes.*

Counsel: *Then over the page, you referred to this a couple of times in your evidence, about meeting the requirement of a person aggrieved, isn't that right?*

Mr Golian: *Yes.*

Counsel: *And is that what Mr. Scott Larsen appears to have been addressing in his affidavit?*

Mr Golian: *Yes….*

[Counsel brought Mr Golian back to the letter from Morris, Nichols, Arsht & Tunnell of the 10th September 2002 and counsel continued as follows.]

Counsel: [A]*t the very end of the paragraph the opinion that's being offered by the lawyers is that BMS Pharma is a successor in interest to the business of DuPont Merck Pharma, isn't that correct?*

Mr Golian: *Yes, I see that.*

Counsel: *Not to its patents or anything of that nature, but to its business, isn't that correct?*

Mr Golian: *That's correct.*

5. The Inventor Assignment

268. Turning to the inventor assignment of 3rd November 2001 (the inventor assignment) and later assignments, the following exchange occurred between counsel for BMS and Mr Golian:

Counsel: [C]*an I ask you to look at the second paragraph: For value of the consideration, the receipt and adequacy of which is hereby acknowledged and in fulfilment of our pre-existing obligation of assignment....What is that a reference to in your view, Mr. Golian?*

Mr Golian: *That's in reference to their employment agreement….*

Counsel: [C]*an you just confirm to the court that as of the date of...*[the] *assignment* [of 2007] *Pharma was registered as the owner of the patent?*

Mr Golian: *Yes.*

6. Emails of October 2001

269. Counsel for BMS brought Mr Golian next to the email of 24th October 2001, at which point the following exchange occurred between counsel for BMS and Mr Golian:

Counsel: *Can I just ask you to confirm what the subject matter of the email is at the top?*

Mr Golian: *Subject is "legal ownership of patents & trademarks".*

Counsel: *Then if I could bring you down to the introductory paragraph before with you deal with each of the various businesses. And you will note on the second and third...*[line] *it says "Please let us know if any of our recommendations for legal entity registration of these intangibles doesn't make sense from your perspective." Did you have any regard to that reference to "legal registration" or did it influence in any way your view articulated to the Court that you believe this was referring to legal title?*

Mr Golian: *Yeah, I think that we have the inventors, by virtue of that employment agreements executing an assignment from the two inventors to BMS Pharma.*

7. The BMS Manual

270. Turning next to the email of 12th June 2002 (the Dora Lynch/Manual Email) circulating the BMS manual, the following exchange occurred between counsel for BMS and Mr Golian:

Counsel: *Can I just ask you to confirm what subject is given in the e-mail?...*

Mr Golian: *The subject is "administrative training manual".*

Counsel: *And then at the bottom of the page you drew the Court's attention to this about the requirement of uniformity and consistency and the manual was written for a definitive reason, and not for reinventing the wheel….From your recollection at the time when you joined in July 2002, did that represent, the effort to achieve uniformity and consistency, represent a goal in the Patent Department?*

Mr Golian: *...So I joined in July 2002, which is just a few weeks after this June 12 email from Dora Lynch. So, she's at least expressing a view that there's a desire to establish more uniformity and consistency, to use her language....*[T]*hat's a desire which I'm sure continued when I joined a few weeks later."*

7

Some Conclusions

i. General

271. What key conclusions might be reached following a consideration of the evidence of Mr Brown, Ms Leung, and Mr Golian. It seems to me that the following conclusions might safely be stated:

[1] the evidence supports BMS's case that from the very beginning of its acquisition of what has become BMS Pharma it exercised centralised control vis-à-vis the intellectual property that it obtained upon the acquisition of Du Pont Pharmaceuticals;

[2] so far as the emails of 24th October 2001 are concerned, Ms Leung was clear and definitive as to the measures for the replacement of directors and officers in Du Pont Pharmaceuticals that were established in advance of the acquisition: In the context of her e-mails of 24 October 2001, Ms. Leung testified in relation to measures put in place prior to the completion of the acquisition for the replacement of directors and officers of the acquired entities.

> [In this regard the following exchange between counsel for BMS and Ms Leung might usefully be noted:
>
> Counsel: *Can I ask you, would you just confirm to the Court, why were you doing this six weeks before the transaction closed?*
>
> Ms Leung: *Well, again, this is standard practice, standard practice for situations where we acquire a new company. We wanted to be sure that we are in a position to establish BMS Pharma Company with employees of BMS Co, listing all the directors and officers who were employees of BMS Co. And this was in anticipation of the filings that we needed to make in the State of Delaware to establish the subsidiary.'*

[3] the rationale for these measures was the assumption of ownership of the assets of acquired entities.

> [In this regard, the following exchange between counsel for BMS and Ms Leung (which occurs immediately after that quoted in the immediately preceding court note) might usefully be noted:
>
> Counsel: *And just in that context, why was it the practice of BMS Co to replace the directors and*

executive officers of companies it was acquiring?

Ms Leung: *Well, it was to be clear that we, Bristol-Myers Squibb Company, own the assets of the new company and we didn't want there to be any ambiguity with respect to that. And again, this was standard, longstanding practice at BMS in an acquisition situation.*]

[4] in the closing exchange with counsel for Teva during her cross-examination Ms Leung "*vehemently disagree*[d]" with the proposition that she was incorrect in her evidence as to (i) how BMS controlled its subsidiaries and owned the assets of those subsidiaries, (ii) her testimony as to control and ownership of BMS subsidiaries, including BMS Pharma; however, she accepted that there were "*special situations*" where the general approach might be departed from.

[In this regard the following exchange occurred between counsel for BMS and Ms Leung:

Counsel: *I have to suggest that your evidence of yesterday with respect to how BMS controlled its subsidiaries and owned the assets of these subsidiaries, that that evidence is not correct and that the proposition you have put forward in relation to control and ownership in respect of these subsidiaries, including BMS Pharma, is incorrect*.

Ms Leung: *I vehemently disagree with you on that point. As I testified yesterday, there could be special situations, as apparently BMS Ireland Holdings is one of them, where we may have taken a different approach, again for good business reasons.*]

[5] Ms Leung's testimony concerning BMS Pharma is entirely supported by contemporaneous materials such as the October 2001 emails, emails between January and March 2002, and the BMS manual. As counsel for BMS put it in their closing written submissions, "*All of these documents point to control emanating from BMS Co as regards what was done as regards intellectual property connected to BMS Pharma.*"

[6] no documents were put to Ms Leung that were inconsistent with centralised control being asserted and exercised by BMS Co over BMS Pharma upon and from the acquisition of Du Pont Pharma (later BMS Pharma).

[7] missteps in this control process do not obviate the general process whereby control was typically sought to be exercised and deployed.

[8] Ms Leung's evidence was fully corroborated by that of Mr Golian.

[In this regard, I recall the following exchange that took place between Mr Golian and myself:

Judge: *Could I just ask: In terms of good corporate governance, how does a policy get approved in*

BMS? Does it go to the executive team or does it go to the Board or how does it happen?

Mr Golian: *So, I would say when I joined BMS in July 2002, there was a pre-existing practice of, from time to time, BMS would acquire other companies and the practice was, generally speaking, that that newly acquired company would become a subsidiary of BMS Company. And just as we had here with what became BMS Pharma, it would be BMS Co that would make decisions with respect to, not only intellectual property, but other aspects of managing that newly acquired company. So, I would say that the policy was really reflected in a practice that had been occurring well before I joined BMS.*]

[9] though, as will be seen later below, I question the usefulness of Dr Rasser's evidence, I note that (helpfully for BMS) he at least confirmed that a process of centralised control is not something that is or was unique to BMS.

[Speaking to his experience of how matters operated within the Procter and Gamble group. the following exchange occurred between counsel for BMS and Dr Rasser:

Counsel: *So, when you acquired a company, you ensured that that policy was carried out, isn't that correct?*

Dr Rasser: *Yes, that is correct.*

Counsel: *And would it be fair to describe that structure as centralised control by P&G parent in respect of its subsidiaries, whether acquired or existing?*

Dr Rasser: *Sorry, could you repeat the question please?*

Counsel: *Would you accept that that is a description of centralised control by the parent over its subsidiaries and the intellectual property of those subsidiaries?*

Dr Rasser: *Oh, yeah, I fully accept that. And clearly, the parent company had that power. My point mainly is that for proper implementation, we had to make sure that the paperwork was in place to reflect that.*

Counsel: *No, no, and I understand that. And what you did as Chief Patent Counsel and what your General Counsel did is you ensured that you managed the intellectual property and in particular the patents of existing or any acquired subsidiaries so that they were residing in the parent, isn't that correct?*

Dr Rasser: *That is correct, yes.*

Counsel: *And then on occasions you managed that IP and those patents as necessary to transfer them or assign them to subsidiaries to facilitate them bringing court cases?*

Dr Rasser: *That is correct, yes.*

Counsel: *And can I suggest to you, therefore, that the type of centralised control that you're talking about is the type of centralised control in the BMS companies, as described by Mr. Golian, Ms. Mathias and Ms. Leung, save that the IP was being put somewhere other than where you would like it to have gone if you were applying the P&G model?*

Dr Rasser: *I certainly recognise and respect the centralised control. I would not agree with your wording that I would have preferred the assignments to have gone to the parent company rather than BMS Pharma. I have no preference for that. My sole point is that you make a choice and then you have to make sure that the other things you do are consistent with that.*]

[10] the upshot of what I have styled the 'in-house evidence' is that BMS Co was able to control the intellectual property rights that it acquired upon the acquisition of DuPont Pharma (now BMS Pharma) and direct where they should rest at any particular time.

ii. Some Aspects of the Closing Submissions

[1]. The Words 'Legal Theory'

272. I note that in its closing submissions, Teva submits as follows:

"*1.11* *That the overlay of beneficial ownership is a retrospective construct is now plain. The notion that BMS Co. might be a beneficial owner of US165 was only raised following a request to the late Mr. Justice Holland from WilmerHale following the discovery there was no assignment to BMS Co., despite "extensive searches"*[12]*. The reason for those extensive searches has never been explained. Mr. Justice Holland's Report was dated 29 June 2021; the first proceedings challenging priority were filed on 9th September 2021, in Italy.*

1.12 *Tellingly, Ms Leung introduced the term, a 'legal theory,' in a discussion as to when BMS first identified the legal basis for BMS' priority claims. It seems undeniable that this "theory" was first identified by the late Justice Holland in June of 2021. Certainly, Ms Leung was unable to point to any other document canvassing a theory of beneficial ownership of US165 before that. (Ms Leung, 'I don't know if – I don't recall any other document in which I've read that, so I've no reason to believe that's not a true statement')*".

273. As to §1.11, with respect the evidence before me from Ms Leung points to the beneficial ownership point as having long been subscribed to by BMS. The best that Teva has come up with in this regard is Dr Rasser's evidence that they were more careful about matters in Procter and Gamble. But I am dealing with a case that involves BMS, not Procter and Gamble; and I do not accept that because Procter and Gamble is said to have done things one way, I should somehow look adversely on in-house evidence that BMS historically did things a different way: different

companies approach similar tasks in a different way; that is the essence of a free market economy. Nothing arises from BMS looking for assignments or not explaining in its evidence why it did so. It does not take great insight to deduce that it likely looked for the assignments because that would make its life easier, and counsel for BMS seemed to intimate as much when he observed in his closing oral submissions that "[T]*here's been lots of straw men in this case; it was said why is Justice Holland referring in his report to a search for an assignment? It's obvious. If an assignment existed, then they* [BMS] *didn't have to worry about it*." As for the timing of Mr Holland's advice, none of us know (except BMS) what was discussed with Mr Holland. But it beggars belief that one would point to the timing of Mr Holland's report (which Ms Leung's evidence would suggest merely confirmed a point of view long held by BMS) as somehow demonstrating that the moment he identified a particular point of law was the moment that point of law first occurred to his client. If I give legal advice to a factory owner today and advise that it is not a good idea from a legal perspective to have unprotected walkways near open vats into which someone might fall, it does not follow (I am not even sure that it can reasonably be contended to follow) that the moment I give that advice must be the moment when that point first occurred to the factory owner.

274. As to §1.12, that point derives from the following exchange, while Ms Leung was under cross-examination:

Counsel:	*Are you telling the court that you've come here to give evidence having proactively managed this litigation and you're not in a position to say whether there is any other basis in this case for claiming priority other than beneficial ownership?*
Ms Leung:	*Yeah, I'm saying that I can't exclude anything. I can't – as I sit here now, I can't say there's absolutely no other* ***basis****.*
Counsel:	*Presumably if there was another basis, you would have explored that with your lawyers?*
Ms Leung:	*I've had many discussions with my – with the lawyers with respect to preparing for this litigation.*
Counsel:	*Okay. And did anybody suggest to you there was some other basis for claiming priority, other than beneficial ownership?*
Ms Leung:	*I don't recall anyone mentioning another* ***basis****. I do recall, without getting into – I don't want to get into attorney-client privilege.*
Counsel:	*No, I'm not asking you for the substance, I just asked you that question, do you recall anybody saying to you there was another basis?*
Ms Leung:	*Another* ***basis*** *other than beneficial ownership?*
Counsel:	*Yeah.*
Ms Leung:	*I don't recall another legal* ***theory****. But I do understand that this is the way BMS acted and this is the way, and we've acted consistent with the longstanding* ***policy****.*
Counsel:	*So, as far as you're concerned, there was no other legal theory that might sustain a priority claim here, is that correct?*
Ms Leung:	*I don't recall a specific discussion regarding another theory*.

[Emphasis added]

275. A few points might be made in this regard. First, I am not convinced that it is generally an especially helpful exercise to start parsing the precise prose deployed by a witness in the course of oral testimony. The spontaneity of oral testimony tends to yield a certain laxity in terminology even in the most careful of witnesses. It is true that Ms Leung used the word 'theory', rather than 'basis'; however, I do not see that these proceedings, whether as to priority or otherwise, turn on the exact word used by Ms Leung in this regard. Second, it is true when one has regard to the above-quoted text that her use of the word "*theory*" (notwithstanding her use of the word "*another*") is really focused on whether there was some alternative basis. Third, what is overlooked by Teva in its

closing submissions is that when counsel started repeatedly used the word 'theory' around this point of his cross-examination, the following exchanges occurred with Ms Leung:

(a)

Counsel: *And is there any other lawyer that you can identify within BMS who had this theory of beneficial interest?*

Ms Leung: *I don't know what you mean by theory of beneficial interest. What I do know is that we continuously held and controlled the IP that we acquired from DuPont*.

[So, a clear rejection by Ms Leung that the control point is some legal theory: she is testifying to the reality of matters as they are and were 'on the ground' within the BMS group],

(b)

Counsel: *And in the statements before this Court from BMS witnesses, you were the first to mention this theory.*

Ms Leung: *You know, I've no reason to believe that's not true. But when we say theory, I can testify as to – and I am testifying – as to exactly how we conduct our business and how we control these assets.*

[So again a clear rejection by Ms Leung that the control point is some legal theory: she is testifying to the reality of matters as they are and were 'on the ground' within the BMS group],

(c)

Counsel: *...I suggest no company of the status of BMS would ever have formulated, much less relied on, a policy of beneficial ownership which, at best, was fact dependent and was a matter capable of dispute.*

Ms Leung: *I disagree.*

Counsel: *I see. So, it's consistent with the mission statements, the corporate statements of BMS that it would take a risk with regard to its most valuable assets on the basis of a legal theory, as you have described it –*

Ms Leung: *I have not described it as a legal theory, you have.*

Counsel: *Well, we beg to differ. On the basis of a legal principle which nobody had advised on, which nobody had assessed and which you yourself, as the person ultimately responsible, had no means of assessing, because you lacked the expertise, and it did that until, at the earliest, Mr. Justice Holland gave a statement in 2021.*

Ms Leung: *As I said, what I'm relying on is years and years of company policy and practice.*

[Ms Leung, with respect, was wrong: she did use the term "*legal theory*"; however, the key point is that yet again, for a third time, she clearly rejects that the control point is some legal theory and makes the point that she is testifying as to reality of matters as they are and were 'on the ground' within the BMS group. So yes, she used the word "*theory*". However, we are all guilty of occasional inexactitude in spoken language. That is the nature of spoken language, even when it is spoken in the witness-box. It is clear

from Ms Leung's testimony that despite her use of the word "*theory*" she was careful to make the point repeatedly that she was testifying as to the reality of matters as they are and were 'on the ground' within the BMS group, not to some legal theory belatedly invented because it suited BMS to do so.].

[2]. The Mistake

276. In the course of Ms Leung's cross-examination on Day 10, the following exchange occurred between counsel and Ms Teva:

Counsel:	*Ms Leung, I just want to ask you one question first. I think you were here in court yesterday when Mr. Golian acknowledged that the application for 652 should've been made by BMS Pharma?*
Ms Leung:	*Correct.*
Counsel:	*And have you discovered since how that mistake came about?*
Ms Leung:	*I don't know how it happened. I'm disturbed to learn that it happened. It was clearly a mistake and it was contrary to the directions of the policy of the company.*

277. Given this exchange, I was a little surprised to read in Teva's closing submissions that the last-quoted text above was "*was a novel revelation, on Day 10 of the hearing, which had never been previously stated in the international litigation relating to this Patent, some of which has concluded*." Quite clearly, the evidence of Ms Leung relates back to evidence that was given on Day 9. So what was it that Mr Golian said on Day 9 that led to the above exchange between counsel and Ms Leung? Counsel is referring in this regard to the following exchange, as described previously above, between another of the counsel for Teva and Mr Golian:

"*Counsel for Teva brought Mr Golian to a summary table prepared by Teva's solicitors showing various (43) PCT applications and whether or not they were effected in accordance with the manual. At this juncture the following exchange occurred between counsel and Mr Golian:*

Counsel:	[M]*y solicitors have prepared a table which summarises .... 43 PCT applications*....[a]*nd the ones identified in pink are all in the name of BMS Pharma; the ones in yellow are in the name of BMS Company; there are two in the name of BMS Company Patent Department; and one is in the name of BMS Medical Managing Inc*.... [I]*f you just take it that that is the position, Mr. Golian, can I ask you to agree with me that that sometimes the guidance in the manual was implemented?*
Mr Golian:	*Yes, I agree*....
Counsel:	*And sometimes…was not.*
Mr Golian:	*Yes, I agree.*
Counsel:	*And do you agree with me that there was, therefore, an inconsistent approach to PCT applications claiming priority in the year following the acquisition of DuPont?*
Mr Golian:	*I would say that …the guidelines, the guidance was not always followed. I had a chance, because I had a little time, to review the tab 3 PCT applications. There were 38 of them. And I didn't get a chance to review the index which has 43… [because it] was*

Monday night. But with respect to tab 3, as I mentioned, there are 38 PCTs. And by my count, 20 of them followed the guidance in the Blair Ferguson email and the paralegal manual, which leaves 18 that did not. And for the 18 that did not follow the guidance, there were three practitioners that did not follow the guidance. So, three practitioners/18. Whereas with respect to the 20 that did follow the guidance, that included nine different patent attorneys. So, in preparing for my evidence today, I just found it notable that there were three people that seemed to not follow the guidance, although even those that didn't follow the guidance, they sometimes did….

Judge: *I assume their defence will be it was guidance, not an instruction* [?]....

Mr Golian: *I think it reflects what we have at this time; we have DuPont Pharma being acquired by BMS, lots of people leaving the organisation, a very significant integration, as we've discussed this morning, a large patent portfolio. And it's the patent attorney's job to get this right, this is important. But somehow, between the paralegal and the patent attorney, it wasn't always done the way the guidance said to do it. It's probably people using templates that say BMS Co were working in some sort of software generating thing that says BMS Co. And again, 20 times the guidance was followed, 18 it wasn't. Was it a mistake? I can only speculate.*

Counsel: *So, you really don't know why that happened, isn't that right?*

Mr Golian: *That's right.*"

278. I suspect that all large commercial institutions to some extent suffer from the problem that even in the face of company policy there will be some staff members who for one reason or another fail to comply with a particular policy, no matter how rigorous or important the policy may be. Be that as it may, Teva sought to capitalise on this deficiency in the following terms in its written closing submissions, describing it (as mentioned above) as "*a novel revelation*", "*never...previously stated*" and "*an extraordinary state of affairs*", continuing:

> "3.*48 There has been no investigation as to how the mistake occurred.....Many of the relevant employees are still employed at BMS....The patent attorney who signed the PCT application...is still employed by BMS Co....*
>
> *3.49 Repeatedly, Ms Leung dismissed the significance of BMS' failure to follow the policy, its failure to notify its experts of its mistake, and its failure to investigate the alleged mistake, maintaining that these matters did not "detract"* [92] *from the main point of what the company's policy was*."

279. Not mentioned by Teva is that Mr Chandler, the distinguished independent expert witness on Delaware law called by BMS made perfectly clear, in the below-quoted exchange during his examination-in-chief, that none of this would have the slightest impact on matters from a Delaware law perspective:

Counsel: *Can I just ask you, insofar as your assessment of this case is*

concerned, it was suggested by [counsel for Teva]*...yesterday that it was a major omission in providing instructions to any expert in this case not to tell them that the judgment made by the client was that a mistake had been made in respect of the later filed patent that was claiming priority from the first filed patent. Have you any observation to make about that?*

Mr Chandler: *The only observation I would make is that it doesn't affect or change my ultimate opinion, or that of Justice Holland's, in my judgment. Because we're being asked to opine whether, under Delaware law, BMS Co is the ultimate true owner of the patent in dispute. And so those issues about mistakes being made wouldn't affect the way a Delaware court would analyse, the legal framework that it would use to analyse is a party – in this instance BMS Co – the true beneficial owner of an asset that's legally titled in a separate entity. It wouldn't affect that analysis, so that's why I say it doesn't change my opinion and wouldn't affect my opinion or that of Justice Holland.*

280. I cannot but respectfully conclude that insofar as Teva has sought to make much of the mistake identified by Mr Golian, accepted by Ms Leung to present, and described by me above, it has little or no relevance insofar as the priority issue in the case before me is concerned.

[3]. Case T0590/98 *Radiopharmaceuticals/AMERSHAM PLC* (ECLI:EP:BA:2003:T059098.20030430)

281. Case T0590/98 concerned the question of whether BMS Pharma could appeal a decision from an opposition commenced in the name of the DuPont Merck Pharmaceutical Company. So, just to note, it did not, *e.g.*, concern the issue of whether BMS Co had a beneficial interest in the intellectual property of BMS Pharma as a matter of Delaware law. The materials supplied to the Technical Board of Appeal in that case were clearly understood by the Board to establish that BMS Pharma Co was one and the same entity as the previously named DuPont Merck Pharmaceuticals company. Nonetheless, in its written closing submissions Teva has made the following observations in respect of that case:

"*4.1 It has now emerged that BMS Pharma represented to the EPO, before and after the Filing Date for the Patent, that it was the owner of all assets worldwide. This is obviously inconsistent with the case now made by BMS, i.e. that BMS Co. owns all the assets of BMS Pharma. Teva relies on the evidence presented by BMS Pharma to the EPO as a matter of fact.*

4.2 By Opinion dated 10 September 2002, addressed to the EPO, Walter Tuthill of Morris Nichols Asrhst & Tunnell, on behalf of BMS Pharma opined that 'BMS Pharma is a successor in interest to the business of DuPont Merck Pharma.' The Opinion refers to the Partnership Agreement at §2.6 which states that all assets and properties owned by the partnership shall be held and recorded in the name of the Partnership and shall be deemed to be owned by the Partnership. The Opinion refers to the Purchase Agreement dated 7 June 2001 and BMS Pharma's agreement to be bound by the Partnership Agreement. The conclusion reached is that the business of DuPont Merck Pharma has been continued by and is vested in BMS Pharma, and BMS Pharma constitutes a successor in interest to the business of DuPont Merck Pharma.

*4.3 The Opinion was accompanied by an Affidavit of Dr. Scott Larsen, sworn on behalf of BMS Pharma on 10 September 2002, which stated, 'the DuPont Merck Pharmaceutical Company, it successor in **business assets**, DuPont Pharmaceuticals Company, and its successor in **business assets**, Bristol*

Myers Squibb Pharma Company have continuously, without interruption been in the business of .... since 1995.' BMS failed to make discovery of this Affidavit.

*4.4 By further letter dated 22 November 2002 to the EPO, BMS Pharma's German lawyers, stated emphatically, 'In fact, as uniform successor in law, [BMS Pharma] became **the owner of the IP rights held by [DuPont Pharma Company] worldwide and is still owner of said rights**' and 'the IP rights of [DuPont Pharma Company] are held by [BMS Pharma].' The letter relied on certain attachments as attesting that BMS Pharma was the owner of the IP in question. BMS failed to make discovery of this Letter.*

4.5 One of the attachments upon which BMS Pharma relied was a second Affidavit of Scott Larsen sworn on 21 November 2002, wherein Mr Larsen swears that 'As a result of the acquisition of [DuPont Pharma Company's] business assets by [BMS Pharma], that [BMS Pharma], acquired the patent rights of [DuPont Pharma Company's] patent estate, including the radiopharmaceutical assets and continues to hold said rights.' (§5) BMS failed to make discovery of this Affidavit.

4.6 Dr Larsen relied at §7 on a Recordation of Assignment with the USPTO dated 'reel/frame: 012607/0038; and recordation date of: 2/11/2002,' which, he says 'evidences said present ownership by [BMS Pharma]' of four patents listed on Schedule A thereof.

4.7 The Recordation of Assignment, upon which Dr Larsen relies, recording the name change from DuPont Pharma Company to BMS Pharma, is the same one that forms part of the chain of title for US165. It records a conveyance by change of name of IP at Schedule A (patents) and Schedule B (patent applications). It is signed by Denise Bierlein, and Blair Ferguson. The patents to which Dr Larsen refers are in Schedule A. Mr Golian confirmed that US165 is listed at Schedule B of the same Recordation.

> *Q. Can you confirm that is US 165 that we've been talking about?*
> *A. Yes.*

4.8 BMS Pharma also relied on an Affidavit of Nadine Flynn sworn on 21 November 2002 confirming BMS Pharma's ownership of certain trademarks. BMS failed to make discovery of this Affidavit.

4.9 These matters were submitted to the EPO by BMS Pharma in opposition proceedings. They culminated in a decision of the Board of Appeal that BMS Pharma was entitled maintain opposition proceedings initially commenced by Du Pont Merck Pharmaceutical Company. (See, Decision T-0590/98.)

...

4.12 Here, the averments and Opinions tendered by BMS Pharma are not qualified...in any way. They are clear: in November of 2002, BMS Pharma was the "owner" of the entire "patent estate", the IP rights "world wide", and the "business assets." This necessarily includes US165. It is unconscionable that BMS would marshal one argument to the EPO and an opposite argument to this Honourable Court, on the same documentary record."

[Teva's emphasis]

282. Sometimes when somebody has much to say about something the assumption can arise that there must be much to be said. That, with all respect, is a danger that seems to me to present when

it comes to the just-quoted submissions. As I mentioned above:

(i) Case T0590/98 concerned the question of whether BMS Pharma could appeal a decision from an opposition commenced in the name of the DuPont Merck Pharmaceutical Company,
(ii) Case T0590/98 did not, *e.g.*, concern the issue of whether BMS Co had a beneficial interest in the intellectual property of BMS Pharma as a matter of Delaware law,
(iii) the materials supplied to the Technical Board of Appeal in that case were clearly understood by the Board to establish that BMS Pharma Co was one and the same entity as the previously named DuPont Merck Pharmaceuticals company.

283. Having regard to what I have stated in the immediately preceding paragraph, I cannot discern any relevance between Case T0590/98 and the matter now in issue before me, namely whether BMS Co had the beneficial interest in US 165 on 17 September 2002 when it applied to file WO652.

[4]. Discovery

284. The issue of discovery was touched upon with Ms Leung. Additionally, in its written closing submissions, surprisingly perhaps at the end of substantive proceedings, Teva makes complaint that certain documents that ought to have been discovered to it were not discovered to it. I do not know whether or not this is so. But there is not an awful lot for me to do at this juncture. This is because in its written submissions, Teva observes as follows:

"*10.42 Given* [what Teva alleges are] *the ongoing deficiencies and the emergence of further inconsistencies on key discovery questions, there is a real imperative that Teva should not bear any liability for BMS' default and conduct. It is submitted that the correct and just order in the circumstances, is that BMS should – at a minimum – be ordered to reimburse Teva for the costs associated with the lost trial dates in 2022.*

10.43 Teva reserves the right to make submissions at the appropriate time as to other forms of orders that are warranted by BMS' conduct prior to and in the course of the trial, including but not only arising from the foregoing failures and inconsistencies."

285. I respectfully decline to make a costs order without first holding a costs hearing (and in so stating I should not be taken to expressly or implicitly acknowledge that there is or is not any merit to the form of costs order that Teva would have me make).

286. I note that Teva reserves the right to make submissions as to such other forms of orders as it would like to be made for "*BMS' conduct prior to and in the course of the trial, including but not only arising from the* [alleged] *foregoing failures and inconsistencies*". Save as regards the discovery-related complaints, I have no idea what conduct is being referred to in this regard, no idea what submissions Teva may wish to make, no idea what BMS may wish to state in reply, and of course no view as to whether any or all such orders as might be sought should be made.

287. I note that among the orders sought by Teva in the discovery motion , some were adjourned to the trial judge (me) which include orders striking out these proceedings. However, there was no request for a strike-out at the hearing of these proceedings or in the written closing submissions that followed. Rather, Teva has submitted that in its view "*It is...correct and just*" – I suspect that BMS holds a different view – "*that BMS should – at a minimum – be ordered to reimburse Teva for the costs associated with the lost trial dates in 2022*". I have given my response to the submission as to costs above. I do not see that I need to adjudicate on the possibility of strike-out (and I see no basis on the evidence before me for such a strike-out) when the party that would be seeking this relief does not appear to be doing so with any assiduity.

IV. THE EVIDENCE OF MESSRS RASSER AND GRANWELL

8

Some Prefatory Observations

288. In the course of his evidence, Dr Rasser was asked (as will be seen) whether *Fujifilm Kyowa Biologics Company Ltd* v. *Abbvie Biotechnology Ltd* [2017] EWHC 395 (Pat.) (considered later below) involved a claim to equitable title where there were undertakings in place rather than assignments. To this, Dr Rasser indicated that he was not familiar with the *Fujifilm* case but that:

> "[T]*he reason we are in court* [was not, as counsel for BMS posited 'because the case-law establishes that, in certain circumstances, a beneficial owner is a successor in title because they don't have a formal assignment' but because]*...someone at BMS did not follow the policy and filed the patent application in the name of BMS Company instead of in the name of BMS Pharma. And that then created a problem when Teva assailed the patent and now the case law on equitable title is being dusted off to try and salvage the situation.*"

289. I must regretfully admit that in a case where Teva (as will be seen) was critical of some of BMS's witnesses, I found this to be a surprisingly partial assertion by an independent expert witness. Unsurprisingly perhaps, after Dr Rasser made the just-quoted observation, counsel for BMS took a degree of umbrage on his client's behalf at what he clearly perceived to be a deprecatory assessment of the position contended for by BMS in the present proceedings as regards equitable ownership of the right of priority.

290. I would but note that the potential for there to be equitable ownership of a priority document that would confer a right to claim priority is a prospect which has repeatedly been countenanced by the courts of the neighbouring jurisdiction and in relatively recent cases that require no 'dusting off'. Four cases, it seems to me, might usefully be mentioned in this regard, namely *KCI Licensing Inc.* v. *Smith & Nephew Plc* [2010] EWHC 1487 (Pat.), *HTC Corp v. Gemalto SA* [2013] EWHC 1876 (Pat.), *Fujifilm Kyowa Biologics Company Ltd* v. *Abbvie Biotechnology Ltd* [2017] EWHC 395 (Pat.), and *Accord Healthcare Ltd* v. *Research Corporation Technologies* [2017] EWHC 2711 (Pat.), each of which I briefly consider hereafter.

KCI Licensing Inc. v. *Smith & Nephew Plc* [2010] EWHC 1487 (Pat.)

291. Here, the claimants were the exclusive licensees under European Patent UK No. 0 777 504 B1 entitled "*Wound drainage equipment*" and European Patent UK No. 0 853 950 B1 entitled "*Wound drainage canister*". 950 was a divisional of 504 and both had a claimed priority date of 22nd August 1994. They sued the defendants for infringement. The defendants denied infringement and counterclaimed for revocation of the patents on the ground of lack of inventive step. The patents concerned apparatus for use in Negative Pressure Wound Therapy (NPWT). NPWT involved packing the wound with a dressing which was then covered by a film to create a seal. A partial vacuum was then applied to the area under the seal. NPWT had been found to reduce bacterial infection and to promote tissue growth, and thus to help heal wounds which were difficult to treat by previous methods.

292. In the course of his judgment in *KCI*, Arnold J., as he then was, referred to a decision of the EPO's Legal Board of Appeal in which the proposition was accepted that although a particular assignment was ineffective in law, the assignee had acquired an equitable interest in the patent application which was a proprietorial interest. Arnold J. then moved on to observe, at §71, that "*When determining whether a person is a 'successor in title'...it must be the substantive rights of that person, and not his compliance with legal formalities, that matter.*"

HTC Corp v. Gemalto SA
[2013] EWHC 1876 (Pat.)

293. This case involved the trial of the validity and infringement issues in actions for the revocation of two patents of the defendants, namely European Patents (UK) Nos. 0 932 865 and 0 829 062, in which Gemalto counterclaimed for infringement. Both patents concerned technology relating to chip cards for smart phones. The alleged acts of infringement concerned certain android mobile phones which had been sold in the UK. In the course of his judgment in that case, Birss J., as he then was, having referred to the judgment of Arnold J. in *KCI Licensing*, observed as follows, at §134:

> "*Mr Mellor submitted that this showed that as long as an applicant had, at the relevant date, what English law would characterise as a beneficial title to the invention, even if the bare legal title had not been acquired, then the applicant was a successor in title in the relevant sense. I did not understand Mr Tappin to dispute that and I think he was right not to. In my judgment if the relevant person has acquired the entire beneficial interest in the invention at the relevant time then that should be enough to satisfy the law.*"

Fujifilm Kyowa Biologics Company Ltd v. *Abbvie Biotechnology Ltd*
[2017] EWHC 395 (Pat.)

294. This was the trial of two actions, in which the claimants had sought the revocation of two granted patents of the defendant, Bermudan company (AbbVie), being the 656 patent and the 322 patent. Both related to the use of adalimumab, which was sold under the trade name HUMIRA, in the treatment of various indications including rheumatoid arthritis and psoriasis. However at the time AbbVie also had a number of pending divisional applications relating to adalimumab pending before the EPO and, relying upon the decision in *Arrow Generics Ltd v. Merck & Co. Inc* [2007] EWHC 1900 (Pat.) the claimants obtained permission to amend to add claims for declarations, in effect, that the claimants' proposed products, administered in accordance with a specified dosage regimen, would have been obvious and/or anticipated for administration for rheumatoid arthritis and for psoriasis and/or psoriatic arthritis as at the priority dates of the 656 and 322 patents respectively. The declaratory relief was sought with a view to clearing the way for the marketing of biosimilar adalimumab products after the expiry of the basic adalimumab patent (the 578 patent) and its associated supplementary protection certificate. If obviousness/anticipation was established, such a declaration would create a squeeze between infringement and validity such that an action for infringement would not succeed in the UK.

295. In the course of his judgment in that case, the late Carr J. referred to both *KCI Licensing Inc. v. Smith & Nephew Plc* [2010] EWHC 1487 (Pat.) and *HTC Corp v. Gemalto SA* [2013] EWHC 1876 (Pat.), noting, at §30, that "*Both first instance judgments were considered by the Court of Appeal in* Idenix Pharmaceuticals Inc *v.* Gilead Sciences Inc. *[2016] EWCA Civ. 1089, where Kitchin L.J. expressed the provisional view that KCI and HTC were correctly decided.*" Notably, when it comes to facts of the present case, in *Fujifilm* Carr J.'s ultimate conclusion that the relevant entity was the successor in title turned on an analysis – underpinned by evidence concerning US and German law – of a series of events and transactions that ultimately depended on there being an ability on the part of that entity to compel the transfer of rights. Thus he observes, amongst other matters as follows, in terms that to some extent resonate with the present case:

> "*63. I find that Knoll AG was KPC's nominee to hold all rights resulting from international clinical research and development, including the Invention. At any time, Knoll AG could have compelled KPC to transfer legal title. Therefore, as a matter of US law, Knoll AG was the beneficial owner of the US inventors' rights in the Invention.*

...

70. *The claimants allege that it is only when a claim is made by an employer that the invention, including the right to claim priority, is transferred to the employer. If the employer makes no claim then the right to priority remains with the employee, who may choose to apply for a patent. They allege that, absent a claim by Knoll GmbH under ArbEG, the right to claim priority had not passed from Dr Kempeni, and therefore, the chain is broken. I do not accept this submission. It appears to me that it is based on compliance with formal technicalities, rather than substance. I accept AbbVie's case that at any time Knoll GmbH had the right to demand delivery of an Invention Report, pursuant to statute, and to claim the Invention. Therefore, as in KCI , Knoll GmbH had the right to compel Dr Kempeni to transfer the Invention to it. In substance, Knoll GmbH was the owner of the Invention, and could exercise its right to claim it at any time.*

71. *I find that when Knoll GmbH entered into the APA with Abbott Bermuda on 29 October 2001, legal ownership of Dr Kempeni's part of the Invention remained with Dr Kempeni, but was subject to the right of Knoll GmbH to claim the Invention. Any attempt by Dr Kempeni to assign any rights in the interim would be invalid as against Knoll GmbH. At any time Knoll GmbH had the right to demand delivery of an Invention Report, pursuant to statute, and to claim the Invention. Therefore, Knoll GmbH was, in substance, the owner of the Invention.*

...

97. ...[W]*hen the PCT Application was filed Knoll GmbH had agreed to transfer all its ex-US rights in US 961 to Abbott Bermuda. Even though the right to compel an Invention Report and then claim the Invention from Dr Kempeni was not transferrable, it could be exercised by Knoll GmbH. At any time after the APA and prior to the filing of the PCT Application, Abbott Bermuda could have compelled Knoll GmbH to claim the Invention from Dr Kempeni and then to transfer it to Abbott Bermuda.*"

Accord Healthcare Ltd v. *Research Corporation Technologies*
[2017] EWHC 2711 (Pat.)

296. This was an action concerned the validity of European Patent (UK) No. 0,888,289 which covered an anti-epileptic drug called lacosamide. The patent arose out of work which had been carried out at the University of Houston in the USA by Professor Kohn and his group, who had been working on anti-convulsant compounds since the 1980s. Although the Patent had expired in March 2017, a supplementary protection certificate provided on-going protection for lacosamide until 2022. The defendant (RCT) was the proprietor of the Patent and its exclusive licensee sold lacosamide for use in the treatment of epilepsy under the brand name VIMPAT. A percentage of the licence fees paid to RCT in respect of lacosamide went back to Houston and to Professor Kohn and his group. Accord, as claimant, contended that the patent was not entitled to the priority date claimed, namely 15th March 1996. RCT accepted that, if priority was lost, the patent was invalid in the light of a paper referred to as Choi. If the patent was invalid, the supplementary protection certificate would be revoked leaving the path clear for generic competition. Accord also contended that the Patent was invalid on grounds of obviousness in any event.

297. In the course of his judgment in that case, Birss J., as he then was, observed, amongst other matters, at §75, that:

> "*I find that the legal principles applicable to priority entitlement are settled at this first instance level....(iii)* [I]*f the local law applicable to rights of the applicant and the patent application at the place and time when it was made allows for a splitting of property rights into legal and equitable interests, then it will be sufficient to establish an entitlement to priority if the applicant holds the entire equitable interest at the relevant date.*"

298. Again, when it comes to Delaware law, the law by reference to which the priority point falls to be adjudicated, I am confronted with the Common Delaware Evidence (which inexorably leads in turn to the Paragraph 10 Point).

9

The Evidence of Dr Rasser

A. Introduction

299. Dr Rasser is an experienced patent attorney and a former longtime 'General Counsel – Patents' at Procter and Gamble. Subject to para.4 of this judgment, an abridged version of Dr Rasser's reports are attached as Appendix 10. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

300. In his initial report, Dr Rasser states as follows (at §1.2):

> "*I have been contacted by solicitors acting for…Teva…to provide assistance on certain facts and circumstances that are known to me based on my background and experience in corporate patent matters as set out below. I have been informed that there are patent proceedings brought by Teva and its relevant entities within the Teva group against BMS Holdings Ireland Unlimited Company…and its relevant entities within the BMS…group in relation to a patent covering the product apixaban across various jurisdictions in Europe*",
>
> and (at §4.6):
>
> "*In particular I was asked to consider the witness statement of Paul Golian dated 21 March 2022 and appendices thereto…submitted in the Irish Proceedings*."

301. I consider hereafter the evidence that Dr Rasser gave under examination, cross-examination, and re-examination. Dr Rasser was a pleasant and engaging witness and clearly a man of achievement. Nonetheless, and this is no reflection on Dr Rasser, I am still at a bit of a loss to know why he was called to give evidence. The beauty of private enterprise and of private property in a free economy is that, provided I act in accordance with law, I may operate my private enterprise as I will and I may do with my private property what I will. So just because BMS may or may not operate its enterprise in a similar manner to other enterprises or may or may not treat with its property in a similar manner to other enterprises is really neither here nor there. In this regard I accept as fully correct the averment of Ms Leung at para.11 of her witness statement (see Appendix 8) where she avers as follows:

> "*11. As an initial matter, it is my view that Dr Rasser's statements with regard to how Procter & Gamble ('P&G') may have been structured, how P&G may have handled IP within its corporate structure, or what was 'very important at P&G' are irrelevant to the situation at BMS. Based on my background and experience, it is my understanding that different corporations may be structured differently, may have different ways of handling IP within their corporate structure, and may have different corporate policies and practices. Accordingly, while Dr Rasser stated that '[a] very important point at P&G was that all of the IP was owned and held by a specific entity, no matter where the invention was made or where the trademark was filed' and '[i]n the case of P&G it was all owned by the parent company,' such are not, and were not during the relevant time, relevant to BMS given its corporate structure and how decisions with respect to IP were and are made*."

B. Examination

1. A Written IP Policy

302. Asked by counsel for Teva whether it was typical in a global pharmaceutical company to have a policy concerning ownership of intellectual property, Dr Rasser indicated as follows:

> "[T]*hat was certainly the case within Procter & Gamble. But as I already indicated, I interacted with colleagues from other companies where we were comparing notes and that was very much, and certainly in the larger companies, it was, I'd say, standard to have a written policy that dealt with the nitty gritty details of obtaining and filing and prosecuting patent applications and things like that…. The policy itself was developed in consultation with other functions within the company, because it was important to be consistent with, for example, the tax structure that we had, so that the ownership of the assets, the patent applications and the patents would be confirmed while the structure that he had for the assets for tax reasons or for other reasons.*"

2. Particular Concerns as to Migration or Transfer of Priority Rights

303. Asked by counsel for Teva whether there are any particular concerns as to the migration or transfer of priority rights in any acquisition setting, Dr Rasser indicated as follows:

> "*During my time at Procter & Gamble we made several acquisitions and the General Counsel would create a task force that would include the tax lawyers and corporate lawyers and an IP lawyer to discuss how the new assets would become integrated….The standard or the default was that everything would be transferred to the parent company, Procter & Gamble company. That typically would take quite a bit of administrative work, but it was felt that it was important to do it that way and to do it quickly and consistently so that again there would be clarity for the entire organisation as to where these assets resided and also to have a transparency for tax purposes as well.*"

3. BMS Pharma as a 'bucket'

304. Asked by counsel for Teva about the observation of Ms Matthias concerning BMS Pharma being a bucket of patent applications into which BMS could dip from time to time, Dr Rasser observed as follows:

> "*I recall that in my time as Chief Patent Counsel at Procter & Gamble in the 1990s, PCT was not generally used by US companies, there was a reluctance to use it. I recall that the United States initially was signatory only to Chapter 1 of PCT and only later signed up to Chapter 2. US companies were sort of carefully treading, because there was a very significant administrative advantage of using PCT, but there were concerns about implications for things like, well, claiming priority. And we didn't know --I mean there is a lot of discussion now about, well, of course it's the law of the country where the transfers took place that should apply; that was not settled law at the time. So, we were concerned about that. And when we started using it, at Procter & Gamble we assigned one person in the organisation, a paralegal, to actually become an expert on PCT and educate the rest of the organisation on PCT. And we were very careful to have written assignments, because we could not predict how foreign countries would deal with a situation where no written assignment was in place. And so, when I read that BMS Company apparently had a different policy at the time, or at least as it was explained in the document by Ms. Mathias, I really couldn't believe my eyes. Because this was about the same timeframe, a little bit later, but not that much, that I was sort of becoming carefully acquainted with PCT. So, it struck me as strange. So, now we*

know, of course, that there was in fact a policy at BMS....From the e-mail correspondence, we know that that was not necessarily clearly communicated. So, there were questions asked: How should we deal with this? And Blair Ferguson, who was the Chief Patent Counsel [it seems from the oral testimony of Ms Leung and Mr Golian that in fact he was not]*, was called upon to make it clear to the troops that this is how we do things. And then there was a very observant person who then said, 'Fine, but then what do we do with the PCT filings, or if it's non PCT filings overseas that claim priority from documents, from earlier patent applications that had been filed by DuPont Pharma?' And so there was a follow up saying that, 'Oh, in that case you should do the PCT filing or the filing claiming priority also in the name of BMS Pharma.' And that's something I recognise. Yeah, you want consistency, you do the name change, fine, but the implication is that you then do the priority claim in the same name. And the implication of that is that you do the PCT filings and the non PCT overseas filings that claim priority, you do those also in the name of BMS Pharma. So, now we have a consistent picture. It took some doing to get that settled and get that communicated, but that's what happened. And then clearly that required then an update of the manual that was used by the patent paralegals so that they knew, first of all they knew what was required, but they also have detailed...instructions of how to implement it. And that is something I recognise from my time at Procter & Gamble. The policy changes were made on a need be basis and that then sort of trickled down through the system and so, it's, to me, very natural that that would then require an update of the manual that was used by the paralegals…. It's all very human, all very recognisable and I really felt home again. But apparently, in this case, that was not followed.*"

4. Typical Role of Paralegal

305. Asked by counsel for Teva about the typical role of paralegal in an in-house patent department, Dr Rasser indicated as follows:

"*Well, patent application filings require an enormous amount of paperwork….The Patent Office has its rules; they want drawing figures provided to them in a specific format…. I mean, it really goes to a lot of detail and the manual does an excellent job doing that. That is it's crucial and it puts -- there is no university training or college training that makes one a patent paralegal. But you look for people who have, well, a good mind and who have attention to detail, who are persistent and consistent and in fact need to have a little bit of calluses on their soles as well, because individual patent attorneys may shrug their shoulders and say, 'What a nonsense, why should we do this?' And they should have the spirit and the spine to be able to push back and say, 'Well, this is how we do it, because that's what the manual says, that's what our policy says.' So, they have a very important role, it's often under-appreciated and because there is no standardised training for it, it requires a lot of attention from, let's say, the Chief Patent Counsel to make sure that that part of the organisation is well staffed and functions well and has the tools to be able to function well and. And the manual, obviously, is one of those tools*."

5. The Role of Chief Patent Counsel

306. Asked by counsel for Teva about the role of the chief patent counsel in an organisation such as BMS (an entity of which Dr Rasser was never an employee, so I believe the question was directed more to the typical role of a chief patent counsel in a large pharmaceutical company), Dr Rasser indicated as follows:

"[T]*he Chief Patent Counsel is the head of the patent function within a company. And the responsibilities will include, well, the filing and prosecution of patent applications,*

setting an IP strategy and making sure that what the IP function does is consistent with things that other functions within the company are doing. It's responsible for the staffing, for the training of the staff, for the budget that comes with it. In some companies, including Procter & Gamble, the Chief Patent Counsel is also responsible for patent litigation, for supervising, hiring out sub counsel, winning the case. But that's not the case in all companies. But all the other functions that I described are typically part of the Chief Patent Counsel responsibility."

B. Cross-Examination

1. Fujifilm

307. Asked whether the *Fujifilm* case involved a claim to equitable title where there were undertakings in place rather than assignments (suggesting, I presume, that there could be a degree of informality to these types of arrangements) Dr Rasser indicated that he was not familiar with the *Fujifilm* case but that:

"[T]*he reason we are in court* [was not, as counsel for BMS posited 'because the case-law establishes that, in certain circumstances, a beneficial owner is a successor in title because they don't have a formal assignment' but because]*...someone at BMS did not follow the policy and filed the patent application in the name of BMS Company instead of in the name of BMS Pharma. And that then created a problem when Teva assailed the patent and now the case law on equitable title is being dusted off to try and salvage the situation.*"

2. Intra- group Implementation of policy

308. Asked about intra-group implementation of ultimate parent policies within the wider Procter & Gamble group, the following exchange occurred between counsel for BMS and Dr Rasser:

Counsel:	*So, when you acquired a company, you ensured that that policy was carried out, isn't that correct?*
Dr Rasser:	*Yes, that is correct….*
Counsel:	*Would you accept that that is a description of centralised control by the parent over its subsidiaries and the intellectual property of those subsidiaries?*
Dr Rasser:	*...I fully accept that. And clearly, the parent company had that power. My point mainly is that for proper implementation, we had to make sure that the paperwork was in place to reflect that.*
Counsel:…	....[W]*hat you did as Chief Patent Counsel and what your General Counsel did is you ensured that you managed the intellectual property and in particular the patents of existing or any acquired subsidiaries so that they were residing in the parent, isn't that correct?*
Dr Rasser:	...[Y]*es*.
Counsel:	*And then on occasions you managed that IP and those patents as necessary to transfer them or assign them to subsidiaries to facilitate them bringing court cases?*
Dr Rasser:	...[Y]*es*.
Counsel:	*And can I suggest to you, therefore, that the type of centralised control that you're talking about is the type of centralised control in the BMS companies….*
Dr Rasser:	*I certainly recognise and respect the centralised control. I would not agree with your wording that I would have preferred the assignments to have gone to the parent company rather than BMS*

Pharma. I have no preference for that. My sole point is that you make a choice and then you have to make sure that the other things you do are consistent with that.

309. Asked whether through intra-group control "*you could finish up in a situation where you have entirely integrated the affairs, assets and property of a company you acquire and make a subsidiary and it would exist only in name*", Dr Rasser indicated that he "assume [ed] that …[was]correct"..

3. Inventor/employer relationship

310. Counsel for BMS and Dr Rasser turned next to a consideration of the inventor/employer relationship in the context of patents and inventions. Having referred to the observation in the email of 25th March 2002 (the email of Mr David Roper) that "*Inventions originating from scientists in the Wilmington area after October 1, 2001 should be assigned to BMS, not BMS Pharma*", the following exchange occurred between counsel and Dr Rasser:

Counsel:	*Now, can I just ask you about that? You've read the manual..?*
Dr Rasser:	*That is correct....*
Counsel:	*Who files the patent in the United States?*
Dr Rasser:	*It's the inventors.*
Counsel:	*And what did Procter & Gamble require the inventors to do after they had filed the patent in their names?*
Dr Rasser:	...[P]*referably we would ask them to sign and assign them before the patent application was filed. That was not always possible. But in cases where the assignment was not signed before the patent application was filed then we made a point of quickly following up and getting the assignments.*
Counsel:	*And that's what the manual addresses when it addresses assignments, isn't that right, Dr. Rasser? It addresses, because it's all about filing, the need to get an assignment and in certain circumstances an assignment and a declaration from the inventors?*
Dr Rasser:	*Correct....*
Counsel:	...[C]*an you also confirm that in the United States the reason an employer with such ease can get an assignment from its employees is because it is an accepted principle in the United States, and, in particular, in Delaware, that employees, when they make inventions, are making those inventions on behalf of their employer?*
Dr Rasser:	*Yes, absolutely.*
Counsel:	*The employer, in other words, in the context of an employee, have a beneficial interest or ownership in the patent that the employee invents in the course of their employment?*
Dr Rasser:	*Yes. And I would say that we make use of that when we file the patent application in the name of the company, even before a written assignment has been signed....*
Counsel:	[D]*o you accept there may be certain circumstances in which you can't assign an agreement? You may not be entitled to do so because the other party to it may not agree to it?*
Dr Rasser:	*It* [the BMS Manual] *doesn't say. It could be that it was considered not worth the trouble, I don't know.*

4. Heightened Integration

311. Turning to situations where there is a very heightened level of integration, the following exchange occurred between counsel (asking questions) and Dr Rasser (answering):

Counsel:	*...I take it that within your experience, Dr Rasser, you would have had situations where acquired companies or existing subsidiaries would be so integrated that there would no longer be a need for their names to be used, save in respect of if we can call it legacy matters?*
Dr Rasser:	*Yes….*
Counsel:	*And in those circumstances, what is happening with that level of integration is the parent company is managing all aspects of what the subsidiary's business was..?*
Dr Rasser:	*That is correct....*
Counsel:	*And it's doing that because it controls and owns all aspects of that business..?*
Dr Rasser:	*That's right…*

5. The Manual and Default References to BMS Company

312. Asked by counsel for BMS about the reference in the BMS Manual to the need to be attentive because the form defaulted to BMS Co, the following exchange occurred between counsel and Dr Rasser:

Counsel:	[I]*t's defaulting to Bristol Myers Squibb Company because that is what the policy is as expressed in the 24 October 2001 e mail, isn't that correct?*
Dr Rasser:	*Well, I would disagree with that because the policy creates two types of patent applications; one type in the name of BMS Pharma and one type in the name of BMS Company. So, having a document default to BMS Company in all cases strikes me as inconsistent with that….*
Counsel:	[Wouldn't it] *be logical to have set up the system in such a way that it would default not to the company that's effectively dealing with legacy issues now, but to BMS Co., the parent* [?]
Dr Rasser:	[N]*ot quite, because you would not want a form to default to one if there's a possibility of two different ones.*

6. Ownership by Correct Corporation

313. Dr Rasser's attention was drawn by counsel for BMS to his own observation in his report where he stated that "[A]*t P&G , it was commonly understood that we needed to make sure that at all times assignments were in place to ensure that the entire ownership of IPRs was indeed in the hands of the correct corporation entity.*" He was then asked whether his reference to "*the entire ownership*" referred to the beneficial and legal ownership. Dr Rasser indicated that it did. The following exchange then occurred between counsel for BMS and Dr Rasser:

Counsel:	[W]*hat that e mail on 24th October 2001, per Mr. Golian and Ms. Leung is speaking to is what it says expressly, "legal entity registration", isn't that right?*
Dr Rasser:	*That's correct.*
Counsel:	*It's not addressing legal title in the sense of suggesting that it's anything other than just the legal title, isn't that right?*
Dr Rasser:	*That is right.*

C. Re-Examination

1. Form of Assignment

314. Asked by counsel for Teva whether the assignment of 3rd November 2001 was:

(i) "*a typical assignment of a patent application*", Dr Rasser indicated that it was,
(ii) "*comprehensive in terms of its drafting*", Dr Rasser indicated that it was,
(iii) the type of assignment whereby the application of the patent could have been assigned, Dr Rasser indicated that it could have been done so, observing, "*I see the two inventors had become employees of BMS Pharma, as a result of the acquisition, but BMS Company could have instructed BMS Pharma to instruct their employees to assign to BMS Company. That could have been done…*", and
(iv) accompanied by a recordation sheet in the name of BMS Pharma, Dr Rasser indicated that it was.

315. Taken by counsel for Teva to the assignment of the 23rd April, 2007, wherein it stated amongst other matters that,

"*BMS Pharma does hereby assign to assignee...*" (BMS Company) "*the entire right, title and interest in all countries of the world in and to the patent application*",

and also that,

"*The said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and re examination certificates to be held and enjoyed by the said Bristol Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and re-examination certificates may be granted and/or issued. This assignment includes the grant by the assignor to the assignee of the right to claim priority for the above patent applications*",

and asked whether this was a typical assignment of a patent, the following exchange occurred between Dr Rasser and counsel for Teva:

Dr Rasser: *Well, what struck me is the reference to any remaining right, when you see that there is -- you see, there is a difference in wording between the assignment of the provisional priority application and the subsequent...so, the priority application has serial number...165 and the subsequent filing -- you see, the assignment of right under the priority application is the entire right, title and interest....And then for the patent applications claiming priority from it, it's any remaining right, title and interest. And that struck me as an interesting difference.*
Counsel: *But in respect of the priority application, that's the 165 application*
Dr Rasser: *That's right.*
Counsel: *It's the entire, right, title and interest?*
Dr Rasser: *Right....the implication being that there was no right sitting elsewhere...*

316. Taken next to his own observation in his report where he states that :

> "[A]*t P&G, it was commonly understood that we needed to make sure that at all times assignments were in place to ensure that the entire ownership of IPRs was indeed in the hands of the correct corporate entity. We accepted that this carried an administrative burden and costs but it was widely seen as an important part of good corporate housekeeping*",

Dr Rasser indicated that such an assignment would be achieved (within Procter & Gamble) in a written instrument of the type just looked at.

317. Taken next to his own observations in his report where he states that:

> "*The structure required an occasional internal transfer of rights to deal with a specific situation. By way of example, for purposes of infringement litigation proceedings outside the US, a national patent would be assigned to the local subsidiary in that country so that the plaintiff initiating the proceedings would be the entity that suffered the damages in that respective country*",

Dr Rasser indicated that such an assignment would be achieved (within Procter & Gamble) in a written instrument of the type just looked at.

2. Priority

318. Turning to the issue of priority, the following exchange occurred between counsel for Teva and Dr Rasser:

Counsel:	*Had the inventors, in this situation, in 2001, assigned their interests in exactly the same terms but to a different assignee, being BMS Company, would there have been any difficulty in relation to the priority issues?*
Dr Rasser:	*No, there would not have been.*
Counsel:	*And likewise, had BMS Pharma, within the priority year, assigned its interest onwards to its parent company, BMS Company, would there be an issue in relation to priority?*
Dr Rasser:	*If they had done that within the priority year then there would not be an issue with the claim of priority.*
Counsel:	*And likewise, if the PCT application had been made in the name of BMS Pharma, the assignee of the inventors, would there be an issue in relation to priority?*
Dr Rasser:	*There would not have been. And that was in fact what was intended by the manual.*

3. Centralised Group Services and Subsidiary Assets

319. Asked whether the fact that an organisation goes for a centralised approach for legal services, with those services being provided by a legal in-house team has any bearing on subsidiary ownership of assets Dr Rasser indicated that it did not.

10

The Evidence of Mr Granwell

A. Introduction

320. Mr Granwell is a distinguished tax attorney who has worked in the public and private sectors over several decades, including a stint in government during the Reagan Era. His evidence was concerned essentially with the tax dimensions/implications of the legal/beneficial ownership construct relied upon by BMS.

321. Subject to para.4 of this judgment, an abridged version of Mr Granwell's written evidence is set out at Appendix 6. I respectfully invite readers of this judgment to read that appendix and then resume reading here. In his initial statement, Mr Granwell states as follows (at §1.4):

> "*I have been contacted by solicitors acting for Norton (Waterford) Limited trading as Teva...to provide assistance as an independent expert given my expertise on US federal tax law. I have been informed that there are patent proceedings brought by Teva and its relevant entities within the Teva group against BMS Holdings Ireland Unlimited Company...and its relevant entities within the BMS...group in relation to a patent covering the product apixaban across various jurisdictions in Europe*",
>
> and (at §4.1)
>
> "*I have been asked to consider the witness statement of Sandra Leung of 2 August 2022…submitted in the Irish Proceedings, given my expertise in US federal tax law, and to provide my comments on the U.S. income tax consequences, assuming the control/beneficial ownership concept outlined therein, were to apply for tax purposes.*"

322. An account of the evidence that he gave when examined, cross-examined, and re-examined follows hereafter.

323. I should perhaps note that while I found Mr Granwell to be an engaging witness I did not consider his evidence to be of especial relevance. As will be seen, his evidence largely focused on the potential international tax difficulties that could arise if BMS's legal/equitable ownership construct is correct. But any (if any) such difficulties are in truth a matter for BMS and/or another judge in another case. My role in this regard is confined to discerning whether as a matter of U.S. or Delaware law the legal/beneficial ownership position, as posited by BMS, holds good. If my findings in this regard yield some level of associated difficulty in tax terms, my respectful response is that that is not for me to resolve.

324. I turn now to consider the examination, cross-examination, and re-examination of Mr Granwell.

B. Examination

1. Separation of Beneficial and Legal Interest

325. Asked by counsel for Teva whether he has previously encountered a separation of the legal/beneficial interest in the context of the placement of assets within the pharmaceutical sector, Mr Granwell answered as follows:

> "*I have not....I have been thinking and thinking...going back to when I was in...Government, about the concept of beneficial ownership and legal ownership. And just to put the point upfront, because I think it's very important, it would totally upset the US tax system, because if you had the assertion that the IP was in a subsidiary, either in Ireland or in Delaware, and the parent was the beneficial owner for tax purposes...that would mean, I think, that all the income would be attributable to the parent under the beneficial ownership concept....Which would mean...that if you had a domestic* [U.S.] *parent company and an Irish direct affiliate who had the legal rights to the IP...but the parent company was the beneficial owner, it would seem to me...*[that] *the parent company would be taxable. Ireland would not get a penny under that theory. That is not the way things work today because if you have...legal ownership in the right company, then the IP return is attributable to that company. So it's a major deviation from what we have going on in the US federal tax system.*"

326. Asked whether he had ever encountered a situation in the context presenting where legal ownership was split from beneficial ownership, Mr Granwell indicated that he had not.

2. Determining where Intellectual Property Assets should Reside

327. Asked by counsel for Teva about the considerations that would apply in determining which companies in a group of companies should be given a particular intellectual property asset, Mr Granwell answered as follows:

> "[T]*he main consideration, I think, is commercial, to protect the asset, to have it administered properly and everything that goes along with that. But from a tax point of view, if the IP is in a particular company, you then have to figure out what is the IP going to be used for. If you have an IP holding company, a domestic company which owns the IP as a holding company, it could licence that IP to an affiliate or a non-affiliate and get a fair return so that the person who is the licensee can produce the product. It could also licence the product to a related person to manufacture the product. It could enter into what we call a cost sharing agreement, which means you transfer, basically, the foreign rights to the IP to an Irish affiliate, which has been done often times here, you're probably aware of that. So, there are many opportunities to exploit the IP. And so it's important that the IP is in the right place in the beginning to figure out what you're going to do next in terms of the exploitation of the IP.*"

328. Asked by counsel for Teva whether he had any comment to make about the placing of the intellectual property rights at play in this case in BMS Pharma, Mr Granwell indicated as follows:

> "*Well, the Pharma own the legal rights to the IP. And so, where I would come in, if I were advising the company, I would say, 'Okay, Pharma's* [got] *the IP, what are we going to do with it?' And I would go from there….But, basically, if it was in Pharma in 2000/2001 as the legal owner of the IP, it would get the return if it exploited the IP directly, if it licensed the IP or if it did other types of activities because our rules said that it is the legal owner of the IP that gets the return. And obviously, from a federal tax point of view, you need to know is the return going to a domestic entity, which, in 2000/2001 would have been subject to tax at a 35% rate, or, for example, if there had*

been a licence of a portion of the IP to an Irish affiliate back then and the Irish affiliate paid an arm's length consideration for the royalty, the rate would have been 12.5%.... And I might just add, from everything I have seen and everything I've done, the whole concept of having beneficial ownership in IP, in a multinational concept, I can't wrap my head around it."

329. It is not clear to me why Mr Granwell was so focused on multinational tax arrangements. I am simply tasked with discerning in this case whether as a matter of U.S. or Delaware law the legal/beneficial ownership relationship posited to exist between two Delaware companies (BMS Company and BMS Pharma), as posited by BMS, holds good. Again, if my findings in this regard yield some level of associated difficulty in tax terms, my respectful response is that that is not for me to resolve.

3. Mr Rossi's Email

330. Brought to the email of 24th October 2001 and the recommendation therein that (as regards patents and trademarks related to the pharmaceutical business) "*Maintain legal ownership in BMS Pharma*", Mr Granwell was asked by counsel for Teva what he understood by this text and what implications that statement has in terms of beneficial ownership. To this, Mr Granwell responded as follows:

"*It means that Pharma is the legal owner of the IP. And from a tax point of view, solely a federal tax point of view, it is entitled to the return. And it has the discretion to do what it will with respect to the IP…. As far as I'm concerned, there isn't any beneficial ownership in a multinational context…*[W]*e don't have the concept of beneficial ownership in a multinational context, it's just alien*".

331. Again, it is not clear to me why Mr Granwell was so focused on multinational tax arrangements. I am simply tasked with discerning in this case whether as a matter of U.S. or Delaware law the legal/beneficial ownership relationship posited to exist between two Delaware companies (BMS Company and BMS Pharma), as posited by BMS, holds good. As I have noted previously, if my findings in this regard yield some level of associated difficulty in tax terms, that is not for me to resolve.

332. Asked by counsel for Teva if there was anything in the just mentioned email of Mr Rossi to suggest that the beneficial ownership resided anywhere other than in BMS Pharma, Mr Granwell answered, "*No. No, not to my knowledge, no*".

333. Asked by counsel for Teva whether, apart from tax consideration the location of an IP asset gives rise to more general regulatory issues Mr Granwell answered as follows:

"[Y]*es, there are regulatory issues. Again, I don't deal with all of that. But the entity that owns the IP may have reporting for various non tax reasons. And from a tax point of view, and from an accounting point of view, that asset would be on the books of Pharma to report it as an asset. It could then take depreciation and amortisation and whatever else might be available under the Tax Code.*"

4. Policy by Email

334. Brought to the 'policy' emails and asked by counsel for Teva whether he had ever seen a similar arrangement in terms of iterating policy, Mr Granwell responded that, "[I]*t seems curious to me, just as an observation, to see something in an e mail, as opposed to some other type of arrangement.*"

335. I must admit that my response to this testimony was rather like my response to the testimony of Dr Rasser, namely just because Mr Granwell has seen things done differently or would expect them to be done differently is – with all respect – neither here nor there. If BMS does things in a particular way, that is the way that it does things, even if others (even indeed if everyone else in the world) might approach matters in a different way. If the suggestion is that BMS is lying to me or misleading me or has been less than forthright with me in describing how it approaches matters, I do not accept that contention: Ms Leung and Mr Golian, who each gave detailed and lengthy evidence as to how BMS does matters (and how it did matters here) were entirely credible witnesses.

5. A Trust Arrangement?

336. Asked by counsel for Teva whether he perceived a trust relationship to present in the circumstances at hand, Mr Granwell indicated that he did not: "*I didn't see anything related to a trust in this multinational structure, which would be very peculiar to begin with.*" With respect, I do not know what the reference to a "*multinational structure*" is meant to connote: at issue before me is a legal/beneficial ownership relationship posited by BMS to exist between two Delaware companies (BMS Company and BMS Pharma).

6. Identification of Owner Company

337. Asked by counsel for Teva about the moment in time when he would expect (in an acquisition context) the company that was to be the patent-owner to be identified, Mr Granwell indicated that he would expect this to be done at the time of the acquisition. My respectful response to this testimony is 'What does it matter if this is what Mr Granwell expects?' His expectations have no impact on BMS's ability to do whatever it wants, whenever it wants (provided it acts in accordance with law and there is nothing to suggest that it did not do so here) – and if it did not proceed as Mr Granwell would expect, then the only conclusion to be drawn from that, with every respect, is that it did not proceed as Mr Granwell would expect.

7. Transfer Pricing

338. Asked about transfer pricing by counsel for Teva, Mr Granwell indicated as follows:

> "*Transfer pricing, or the fair payment for, particularly IP, has been a very contentious issue. And in 1986 the Congress added a sentence to our transfer pricing statute, which is Section 482, which deals with arm's length pricing, to say that with respect to intangibles, the consideration has to be commensurate with the income. The purpose of that provision was to give the IRS our internal revenue service the authority to make adjustments on intercompany transactions either from the US out to Ireland or from Ireland to the US to make sure that the consideration was appropriate for intangibles. And that has been the subject of numerous court cases and they still haven't fixed it correctly. But this regulation which I cite* [in his report, being a Treasury Regulation]*, particularly for a patent and I'm just limiting it to a patent says at this point of time, because it was modified a few years later, that the legal owner of the patent is entitled to the income or is the true earner of the income. And it was modified subsequently to provide more leeway for the IRS to consider it. So, when the acquisition occurred in 2001, Pharma, the legal owner of the IP, whatever it did with the patent, would get the return. There was no ifs, buts and maybes. That is just how it worked. And in this case it was very simple, because you had one company buying an entity of another company without any inputs from other affiliates…. Well again with due respect, and Mr Clarke is a well- known tax litigator in the United States, he goes into a series of cases involving transfer pricing. And that's all fine and good …*[I]*n our case, in the subject matter, there was an acquisition of one company by another company. Nothing else was going on. So, I fail to see the relevance of … discussion of transfer pricing… because in the two years I was focusing on, nothing happened.*"

339. I respectfully accept Mr Granwell's evidence in this regard. I do not see the relevance of transfer pricing to the case at hand.

8. OECD Model Treaty and Double Taxation Treaties

340. Asked by counsel for Teva about criticisms levelled at his statement by reference to the OECD Model Treaty, Mr Granwell essentially indicated that that Model Treaty and International tax treaties are an irrelevance to the case at hand: "*The OECD rules are not US legislation or rules….* [I]*n our case and what I was instructed to do was to deal with two US entities, BMS Company, which is the parent, and this Pharma, which are both domestic entities. So, treaties have no relevance…*". The just-mentioned criticisms were made by Mr Clarke and as he was belatedly withdrawn as a witness, his criticisms have no standing in these proceedings. That said, I respectfully accept in any event what Mr Granwell had to state in this regard.

C. Cross-Examination

1. Placement of Intellectual Property Assets

341. Asked by counsel for BMS whether placement of intellectual property was a matter that only arises where one is at the point of commercialisation and earning money from a patent, the following exchange occurred between Mr Granwell and counsel:

Mr Granwell:	*That's correct. But I mean, the question is, you would, I think, when you're structuring the transaction to try and place it initially in what you believe to be an appropriate entity, there may be circumstances where that changes. But I don't think you would willy nilly put it in some random entity without considering the potential tax aspects of that entity.*
Counsel:	*Well, just to be clear, the fact evidence here is that this was a deliberate decision to leave IP prior to 1st October 2001 in BMS Pharma. You're aware of that?*
Mr Granwell:	*Yes, I'm aware of that.*

342. The point that I understand was being made by counsel at this juncture was that what happened within the BMS group was not the placement of assets "*willy nilly...in some random entity*" but a considered decision on the part of BMS. And it is clear from the evidence of Ms Leung that this was not just a considered decision in one case but a longstanding practice that is typically (albeit not invariably) observed by BMS in acquisition transactions.

2. Substance Over Form

343. Counsel for BMS brought Mr Granwell to a segment of applicable Treasury regulations which essentially allows the US tax authorities to look at substance over form (s.482). The relevant provision states that "[T]*he district director may impute an agreement to convey legal ownership if the conduct of the controlled taxpayers indicates the existence in substance of such an agreement.*" Mr Granwell indicated that "*that sentence wouldn't apply to the subject transaction, because there was nothing to impute. You had one company buying something from another company, two unrelated parties. So, 482 wouldn't apply. And it's just the sentence, it gives the district director the ability to do something, but that is totally without scope in our subject case*".

344. Asked by counsel for BMS whether he meant to suggest that in the context presenting the tax authorities could not look behind a particular company to look at substance over form, Mr Granwell replied: "*For a patent, yes. It's different for stock and other things. But for a patent which gives you a monopolistic right, as far as I'm concerned, it's in Pharma.*"

345. I assume that Mr Granwell is correct in the answers that I have just mentioned. However, I do not see the relevance to the case before me of whether the US tax authorities have the power to look at substance over form in deciding in some instances where tax liability should lie. I am not presented with any questions as to tax liability.

3. The *Anderson* Case

346. This consideration of substance over form led to a consideration of the *Anderson* case, with counsel for BMS drawing Mr Granwell's attention to the following observation of the US Court of Appeal, which counsel posited, is a "*statement of principle, not confined to any particular asset or case*":

> "*The Supreme Court has repeatedly said that taxation is an intensely practical process concerned less with legal formalities than with economic realities and that tax consequences flow from the substance rather than the form of a transaction; that command over property or enjoyment of its economic benefits marks the real owner for federal income tax purposes*."

347. By way of response to this quotation being read, Mr Granwell stated as follows:

> "[I]*f that applied in this case to a patent, as I was mentioning, if BMS Company would have placed the patent in Ireland, what this sentence would say is that Ireland is not entitled to the income, but BMS Company is. I think our multinational community would be rather upset with that. And in my experience, I have never seen sort of the concept of beneficial ownership used for purposes of saying that the beneficial owner of a patent is the way you trigger the income.*"

348. Counsel for BMS led Mr Granwell to commentary on amongst other matters, the decision in *Anderson*, in which it is stated:

> "*From these cases it seems to be quite clear that mere passage of title to income producing property through devices which are valid under state law will not insulate the transferor against federal income tax liability unless the passage of title is accompanied by a complete shift of the economic benefits of ownership, direct and indirect.*"

349. By way of response Mr Granwell indicated as follows:

> "*I would disagree with what you're saying. I have never seen this concept applied. And in terms of multinational planning with patents, if you had this concept apply, it would cause chaos in our whole system, because people get the right to the patent which is a monopolistic right which gives them the protection. I'm not getting into how you enforce the patent, but I don't know what any multinational company would do if the parent company were treated as the tax owner. And again, the question comes: Why would the parent company be treated as the tax owner? You had consideration being paid for the transaction, you're buying a patent as opposed to stock. And I think there's a major distinction there. If you look at all the familial cases, I think it would just cause chaos.*"

350. Pressed on the potential for chaos, Mr Granwell indicated that if this was the law then during his time in government:

> *"...we would have picked it up. But we did things on the basis that it's the legal owner and the transfer and so on and so forth. I mean, this has never crossed my mind. Maybe*

I missed something, but it's just, I find it totally bizarre… I think the whole international tax community would go crazy if that was the correct reading."

351. A few points might perhaps usefully be made at this juncture:

- first, again, Mr Granwell's evidence largely focused on the potential international tax difficulties that could arise if BMS's legal/equitable ownership construct is correct. But my role in this regard is confined to discerning whether as a matter of U.S. or Delaware law the legal/beneficial ownership construct, as posited by BMS, holds good as a matter of Delaware law
- second, if my findings in this regard yield some level of associated difficulty in tax terms, my respectful response is that that is not for me to resolve.
- third, I do not see the relevance to the case before me of whether the US tax authorities have the power to look at substance over form in deciding in some instances where tax liability should lie. I am not presented with any questions as to tax liability.
- fourth, the facts of the *Anderson* case (a tax case) bear no resemblance to the case before me. As Mr Granwell later in his evidence observed, "[T]*he Anderson case is just the parent wanted to give...stock to the kids, but he maintained control of it…..and the IRS said 'Well, you maintained dominion and control, you benefited from all of this, this was not a true gift'*." *Anderson* was not a corporate case; there was no attempt at gifting between BMS Company and BMS Pharma or *vice versa*; and I have not been asked to decide any tax issues.

4. The Decision in *Bausch & Lomb*

352. Counsel for BMS drew Mr Granwell's attention to the following observation in the judgment of Bausch & Lomb:

"*Section 482 authorizes respondent to allocate income between controlled enterprises if he determines that such an allocation is necessary to prevent evasion of taxes or clearly to reflect the true income of the controlled enterprises.*"

353. The following exchange then occurred between Mr Granwell and counsel:

Mr Granwell: *With all due respect, I don't see what this has any relevance to my report. My report was dealing with the acquisition of one entity by another entity, no other transactions were involved. And the question is: Do you have a beneficial owner concept? So, this is your standard transfer pricing case, where there was a licence and you're trying to figure out what the appropriate licensing fee is. And it seems to me totally irrelevant to the instructions I was given. I mean, this is a standard case, there's zillions of these cases, but it has no relevance to what I'm dealing with.*

Counsel: *Mr. Granwell, you refer to this in your report. You refer to Section 482. And you acknowledge in 482 that as of 1994, when this transaction was engaged in, that the District Director could impute a different arrangement to what was legally presented.*

Mr Granwell: *I referred to 482 just to make the point that if you're transferring something overseas, you have to be cognisant of 482. I then cite that true earner concept, just putting in that last sentence for information. There are no facts to support anything you're saying because transfer pricing has to deal with more than one entity. We*

> *have an acquisition of one entity by another entity. Nothing else happened….. I'm just making the point that 482 kicks in when you're doing intercompany transfers. That is not the case here…. The case we are dealing with is one company buys something from another company. End of story. And I think a tax lawyer would say, 'Okay, the patent is in one entity and that's the person that earns the income, because it's holding the patent.' Nothing else is going on. And who else could be entitled to the income in that case?*

354. Like Mr Granwell, I do not see that *Bausch & Lomb* or §482 have any relevance to the case before me. When it comes to the legal/beneficial construct posited by BMS my role lies in discerning whether, as a matter of U.S. or Delaware law, that legal/beneficial ownership construct, *as posited by BMS*, holds good; and as will be seen, I conclude by reference to the expert evidence before me that it undoubtedly holds good as a matter of Delaware law. I understand, of course, why counsel for BMS raised the questions that he did. He did not know what view I would take of Mr Granwell, his report, and his testimony until he read this judgment so he had to seek to 'close out' any issues that I might have considered to present, from Mr Granwell's evidence/testimony .

5. Absence of Chaos

355. Counsel for BMS posited the following "*The purpose behind me putting these various questions to you is …. you refer to chaos. There is no chaos from a taxation point of view, because the Revenue at all times has the power available to it to look behind the form at the substance, whether or not it's an international transaction. Would you agree with that?*" To this, Mr Granwell responded as follows:

> "*It can look behind the substance. But you need to have some abusive thing going on. We have I'm sorry to repeat this, Your Honour one major company buying another, buying an entity of another major company. Where is there any abuse? Where is there anything but just an arm's length transaction?.... One company is buying another company. And believe me, having been in the Treasury department, I'm always trying to uncover things and I have that feeling in private practice. I just say this is an arm's length transaction. And what the consequences are are pretty straightforward. There are all sorts of other crazy iterations where something comes up. There's nothing going on, just I'm buying something from you….I own it and that's it.*"

356. As should by now be clear, Mr Granwell's evidence largely focused on the potential international tax difficulties that could arise if BMS's legal/equitable ownership construct is correct. Again, however, I am 'simply' tasked with discerning in this case whether as a matter of U.S. or Delaware law the legal/beneficial ownership relationship posited to exist between two Delaware companies (BMS Company and BMS Pharma), as posited by BMS, holds good. If my findings in this regard yield some level of associated difficulty in tax terms, my respectful response is that that is not for me to resolve.

6. Allocation of Income

357. When counsel for BMS put it to Mr Granwell that there was no potential for chaos because the US tax authorities have "*ample tools available to them to address an allocation of income which they did not believe reflected reality*," Mr Granwell responded as follows:

> "*If I may say, I was dealing with beneficial ownership, I was not dealing with allocation of income. Allocation of income kicks in if you have something to allocate because of a transaction. There is no transaction. I agree, if you are doing a licence or this or that, you could have an allocation of income. What I was focusing on is one company buys another company, that company has a valuable asset, it is sitting there,*

there's no allocation, there's no anything. And if you were to say that you are then licensing the property to a controlled party and the legal owner is not the taxpayer but the beneficial owner, where nothing is going on to attribute an activity to the beneficial owner for purposes of the transaction, I think chaos would result…. [T]*his is a plain, vanilla transaction. And to say there's just income being derived, that someone else is going to be taxable on it, I just don't understand it. And I can't further explain it, because I just never encountered this.*"

358. I respectfully accept Mr Granwell's point as to the irrelevance of allocation of income in the context presenting. As to counsel's point concerning the absence of potential for chaos, I would simply refer to the observations that I made in the previous section above.

D. Re-Examination

1. The Decision in *Anderson*

359. Brought again by Counsel for Teva to the *Anderson* case, Mr Granwell elaborated upon that case in the following terms:

"[T]*he Anderson case is just the parent wanted to give the stock to the kids, but he maintained control of it….. and the IRS said 'Well, you maintained dominion and control, you benefited from all of this, this was not a true gift'. I mean, there are a zillion of these cases and they have this concept of beneficial ownership control or control over the income. In the multinational world, we're not dealing with beneficial ownership in the tax world….*[T]*hat's a trust and estates private clients things.*"

360. I have already indicated above why I consider the *Anderson* case to be irrelevant to the case at hand. That said, I note again Mr Granwell's reference to the "*multinational world*", whereas I am simply tasked with discerning in this case whether as a matter of U.S. or Delaware law the legal/beneficial ownership relationship posited to exist between two Delaware companies (BMS Company and BMS Pharma), as posited by BMS, holds good. If my findings in this regard yield some level of associated difficulty in tax terms, my respectful response (again) is that that is something for the State of Delaware, its legislature, and its courts to resolve, if in truth there is anything to resolve.

2. Beneficial Interest

361. Asked by counsel for Teva to explain the context in which beneficial interest is looked at (presumably in the multinational tax context), Mr Granwell indicated as follows:

"[L]*et me give you an example, going back, say, to the late 1970s. It was often the case that US persons would like to borrow money from abroad, as opposed to domestically....*[I]*f I'm borrowing money from you and you're sitting here in Ireland, under the statute* [U.S. tax law] *there is a 30% withholding tax when I pay money to a non US person. But if you're a treaty beneficiary and a real Irish resident, it goes down to zero. So, take the situation, you have a wealthy Arab financier to wants to lend money to a United States enterprise. If it did it directly, there would've been a 30% withholding tax. But back then, the Netherlands Antilles was part of the Netherlands...and we had a treaty with the Netherlands Antilles…which permitted you, by fiddling around, to just pay a very slim toll charge to the Antilles and get treaty benefits. So, from the US point of view, that was avoiding our 30% withholding tax. And one of the precepts of our treaty programme was to prevent that. In fact the Antilles Treaty was terminated and we came in with a provision together with what's called portfolio interest, which permits this….So, this was treaty shopping. I mean, I think you can understand what I am saying. And that's where the concept of beneficial*

ownership comes in: are you the person who is entitled to the income and you're not giving it to someone else? You're not giving it to anyone else because, you know, you're you. But if you use some company and you're sitting in, you know, Dubai or something, then you might pass it on one way or the other and there shouldn't be treaty benefits given….[T]*hat was the purpose, to prevent treaty shopping….That has nothing do with what we're talking about here. I mean, it's just a different thing.*"

362. This was interesting evidence and I could have listened to Mr Granwell for a lot longer than he was in the witness box, but he was absolutely right: what he was describing in the last-quoted text "*has nothing to do with what we're talking about here....*[I]*t's just a different thing.*"

E. Mr Clarke

363. Mr Clarke was expected to be called as an expert witness by BMS to deal with much the same area of evidence covered by Mr Granwell (who was called by Teva). Belatedly, when on the cusp of being called to the witness box, Mr Clarke realised that he could not offer himself as an independent expert because he and/or his law firm do work for BMS. This appeared to cause great vexation on the part of Teva. I am not sure why. Perhaps Mr Clarke should have realised sooner than he did that he could not hold himself out as an independent expert witness. But it appears that he did not realise that he was compromised until a late stage; once he did so he told the BMS legal team; and counsel for BMS, once apprised of matters, rightly took the decision that, given that Mr Clarke could not hold himself out as an independent expert witness, he could not be called as an independent expert witness. So be it: life does not run smoothly; it may be that this is an aspect of matters that will be required to be revisited in any future costs application as doubtless Teva incurred legal fees in anticipation of having to deal with Mr Clarke's evidence.

364. I note in passing that the Supreme Court have confirmed that there is no clear judicial authority to support the drawing of an adverse inference from the withdrawal of an expert witness. That point was made in *Doyle* v. *Banville* [2012] IESC 25, a personal injuries case arising from a terrible motor accident which left Mr Doyle suffering from paraplegia. One of the grounds of appeal before the Supreme Court was that the trial judge had erred in law in failing to draw an inference from the failure of the defendant/respondent to adduce expert evidence. In the course of his judgment in the case, Clarke J., as he then was, observed as follows, at §3.5:

"*While there may be cases where an inference can be drawn from a failure to call evidence of fact (see for example* Doran *v.* Cosgrove & anor *(unreported, Supreme Court, 12th November, 1999, Keane J.)), it is not clear that an equivalent inference can properly be drawn from a failure to call expert evidence.*"

V. THE EPC-RELATED EVIDENCE

[Part V should be read in tandem with Part XIII (which was added after the belated decision of the EPO's Enlarged Board of Appeal in Consolidated Cases G1/22 and G2/22, 10th October 2023) and vice versa.]

11

Some Prefatory Observations

365. A reader coming cold to this judgment might perhaps wonder why there is a need for any evidence regarding the European Patent Convention. So it may be useful for me to explain why this evidence fell to be given.

366. Along with its arguments concerning United States federal law and also the laws of Delaware, Teva has contended in these proceedings that s.25 of the Patents Act 1992, as amended (under which the right to priority falls to be considered in this case) effectively imposes a requirement of an assignment of US 165 to BMS Co before BMS Co could be found to have the right to claim priority on the basis of it. It suffices in this regard to quote s.25(1) of the Act of 1992, as amended, which states as follows:

> "*A person who has duly filed in or for the State, or in or for any other state party to the Paris Convention for the Protection of Industrial Property or to the Agreement establishing the World Trade Organisation, an application for a patent or for the registration of a utility model or for a utility certificate or for an inventor's certificate,* ***or his successors in title****, shall enjoy, for the purpose of filing a subsequent patent application under this Act in respect of the same invention, a right of priority during such period as may be prescribed, subject to compliance with any prescribed conditions and the payment of any prescribed fee.*"
>
> [Emphasis added]

367. How does s.25 interact with the Paris Convention and the European Patent Convention? To start with, I note that the impugned patent in this case is a European patent and that, pursuant to ss.119 and 120 of the Act of 1992, as amended, such patents (and applications for them) fall to be treated as patents granted or applied for under that Act. Hence the right to priority in respect of the impugned patent falls to be determined under s.25 of the Act. It suffices for present purposes to quote from s.119(1) and s.120(1)(a) of the Act of 1992. They provide as follows:

(i) s.119(1):

> "*Subject to the provisions of this Act, a European patent designating the State shall, as from the publication of the mention of its grant in the European Patent Bulletin, be treated for the purposes of this Act as if it were a patent under this Act granted in pursuance of an application made under Part II and as if notice of the grant of the patent had, on the date of the publication, been published under section 34 in the Journal...*"

(ii) s.120(1)(a):

> "*An application for a European patent designating the State and having a date of filing under the European Patent Convention shall be treated for the purposes of the provisions of this Act specified in subsection (2) as an application for a patent under this Act having the said date as its date of filing under this Act*."

368. Section 25 implements the right to priority provided for in Article 4A(1) of the Paris Convention, *i.e.* the Paris Convention for the Protection of Industrial Property (1883). The Convention applies to industrial property in the widest sense, including patents, trademarks, industrial designs, utility models, service marks, trade

names, geographical indications and the repression of unfair competition. It has three main plinths which concern, respectively, national treatment, the right of priority, and a few common rules. Art.4A(1) of the Convention, so far as relevant to these proceedings, provides as follows:

> "*Any person who has duly filed an application for a patent...in one of the countries of the Union,* ***or his successor in title****, shall enjoy, for the purpose of filing in the other countries, a right of priority during the periods hereinafter fixed.*"
>
> [Emphasis added]

369. This provision yields a right to claim priority from the date of first filing for any patent filed in respect of the same invention within a year of first filing (under Art. 4C). More generally, the Act implements the European Patent Convention, of which Ireland is a member state. The right to priority is provided for under by Article 87(1) of the European Patent Convention. This states as follows:

> "*(1)Any person who has duly filed, in or for (a) any State party to the Paris Convention for the Protection of Industrial Property or (b) any Member of the World Trade Organization, an application for a patent, a utility model or a utility certificate,* ***or his successor in title****, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application.* "
>
> [Emphasis added].

370. Article 4A(1) of the Paris Convention, Article 87(1) of the European Patent Convention and s.25(1) of the Act of 1992, as amended, all provide that the right to priority shall belong to the applicant for the original filing or the successor in title to same. Thus a key question that presents in this case is whether BMS Co. can be regarded as a successor in title to the right of priority arising from US 165.

371. Curiously perhaps, almost nothing can be gleaned from the express text of s.25 of the Act of 1992 (or indeed Art.87 of the European Patent Convention) regarding successors in title. However, helpful guidance in this regard is provided by Case T1201/14 *(Transfer of right of priority)*, a decision of the European Patent Office's Technical Board of Appeal. That was a case in which, during opposition proceedings the patent proprietor argued that two transfers had occurred. The opposition division did not accept the validity of the second transfer, which the patent proprietor had attempted to substantiate by means of three different lines of legal argument, each based on a different type of transfer, namely a transfer by way of a *nunc pro tunc* assignment under United States law, an implicit transfer under German law, and a direct transfer under United States law. In its decision, the Technical Board of Appeal, at para.3.1.1.3, summarised, in the following terms, "*the substantive requirements derivable from the EPC for a valid transfer of the right of priority*":

> "*The successor in title with respect to the right to claim priority from a first application according to Article 87(1) EPC...must prove that it indeed owned (i) before the filing of the later European application, (ii) the right of priority relating to the first application for the purpose of filing the later European application claiming that priority*."

372. Other cases in a similar vein include Case T-1103/15 *University of Alabama*, Case T-0205/14 *Ibandronate sodium, Form QQ/Teva*, and Case T-1786/15 (*General Hospital*) at §12)).

373. In Case T-1103/15 *University of Alabama* (ECLI:EP:BA:2018:T110315.20180222), the opposition division of the European Patent Office arrived at the conclusion that: (i) the priority of US 326704 P of 3rd October 2001 was not valid; (ii) D3, a document published on 17th April 2002,

before the filing date of the patent in suit (3rd October 2002) was therefore a document according to Article 54(2) of the European Patent Convention for the claimed subject-matter and its content anticipated claims 1 and 5 of the main request. Article 54(2) of the European Patent Convention provides as follows:

> "*The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application*."

374. In the statement of grounds of appeal the appellant did not contest that the main request lacked novelty over D3. The question that the Board had to answer was rather whether the right of priority had been validly claimed to determine whether D3 was a document or not according to Article 54(2) of the European Patent Convention. For present purposes, of note is the observation of the Technical Board of Appeal (at §1.3) that:

> "*According to board of appeal case law, a person who claims he is a successor in title within the meaning of Article 87(1) EPC and is therefore entitled to claim priority has to prove his entitlement where the validity of the claimed priority is at stake*".

375. In Case T-0205/14 *Ibandronate sodium, Form QQ/Teva* (ECLI:EP:BA:2015:T020514.20150618), the appellants contested the entitlement of the patent in suit to the priorities from US applications Nos 60/604, 026 of 23rd August 2004 (P1) and 60/690,867 of 16th June 2005 (P2). They argued that the respondent had failed to prove to the required standard that, on the date of filing of the international application number PCT/US2005/030500, published as WO 2006/024024, the rights of priority derived from the US provisional applications (P1) and (P2), both filed in the name of the three inventors, had been validly transferred to the respondent. As a consequence, the date of filing of the international application WO 2006/024024 was the effective date for determination of the relevant state of the art. For present purposes, of note is the observation of the Technical Board of Appeal (at §3.5) that:

> "*If entitlement to priority is challenged, a successor in title, who desires to take advantage of the priority of a first application and who asserts that priority is rightly claimed from the first application, has to prove its entitlement to that right, which includes a valid transfer of the right of priority*".

376. In Case T-1786/15 *BMP Antagonists/General Hospital* (ECLI:EP:BA:2020:T178615.20201015) the patent proprietor was The General Hospital Corporation. So the case is generally known as the *General Hospital* case. There, the employee-inventors were the applicants for the provisional application from which the patent claimed priority. The General Hospital Corporation filed the Patent Cooperation Treaty application. The inventors were required by D31 (MGH Intellectual Property Policy) to transfer certain IP rights to the Massachusetts General Hospital, the parent company of the General Hospital Corporation. The General Hospital Corporation relied on an internal 'Ownership reallocation policy' (D51) to assert a transfer of priority or equitable title from the parent (the Massachusetts General Hospital) to the subsidiary (the General Hospital Corporation) prior to the Patent Cooperation Treaty application. The Technical Board of Appeal found that the policy did not discharge the burden of proof because it did not provide evidence that it was in fact adopted. For present purposes, of note is the observation of the Technical Board of Appeal (at §12) that "[T]*he appellant, having been the applicant, bears the burden of proof for demonstrating that the reallocation of ownership of the priority took place* [on a particular date]". Of course in the present case, the *General Hospital* case is canvassed by Teva to possess another significance. Thus, the General Hospital Corporation relied on an internal 'Ownership reallocation policy' (D51) to assert a transfer of priority or equitable title from the parent, the Massachusetts General Hospital, to the subsidiary, the General Hospital Corporation, prior to the Patent Cooperation Treaty application. But the problem in the present case, as now repeatedly stated, is that BMS has never sought to rely on a policy as yielding a transfer of

a priority right. Its case in this regard comprised the Control Proposition.

377. A notable feature of the evidence considered in the pages that follow is that while Dr Kinkeldey, who gave evidence on behalf of Teva on this aspect of matters, (i) appeared, in her written reports for the court (see Appendix 7), to support the need for an assignment under Article 87 of the European Patent Convention, she (ii) accepted in her oral evidence that: (a) no such requirement could be drawn from Article 87 itself; (b) the practice at the EPO is to apply national law and that once the right to priority could be accepted under the applicable national law as being owned at the relevant time by the person claiming priority, then no further requirement was imposed under Article 87; (c) this principle extended to equitable ownership and (d) the only relevant question was whether equitable ownership was considered ownership under the applicable law.

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The Evidence of Dr Kinkeldey

A. Introduction

379. Dr Kinkeldey is a patent attorney and a former member of the Boards of Appeal of the European Patent Office. Subject to para.4 of this judgment, an abridged version of her reports is attached as Appendix 7 hereto. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

380. In her initial report, Dr Kinkeldey describes her role as follows:

> "*I have been contacted by solicitors representing…Teva…to provide assistance as an expert on certain facts and circumstances that are known to me based on my background and experience as a European patent attorney and former member of the Boards of Appeal…of the European Patent Office….I have been informed that there are patent proceedings brought by Teva and its relevant entities within the Teva group against BMS Holdings Ireland Unlimited Company…and its relevant entities within the BMS…group in relation to a patent covering the product apixaban across various jurisdictions in Europe*"
>
> and, at §3 of her second witness statement:
>
> "*I make this replying expert witness statement in response to that of Mr. Christopher Rennie-Smith.*"

381. I consider hereafter the evidence that Dr Kinkeldey gave under examination, cross-examination, and re-examination.

B. Examination

1. Questions of Priority Before Boards of Appeal

382. Asked by counsel for Teva to explain how questions of priority are typically addressed before EPO Boards of Appeal, Dr Kinkeldey indicated as follows:

> "*Normally during examination proceedings the question whether rightfully priority is claimed is not an issue, unless, for some reason it jumps to the examiner that something is wrong. But normally not. And it pops up then in, as soon as the cases become inter partes cases….Then the Board have to decide on first the Opposition Division and then it goes into appeal normally, and then the Boards of Appeal have to decide on the priority issue.*"

2. Assessing Succession in Title

383. Asked by counsel for Teva whether there are any substantive requirements applied when assessing succession in title, Dr Kinkeldey indicated as follows:

> "[W]*e do not have any particular prescriptions how we should examine whether or not successor in title was indeed a successor in title….*[I]*t is a question of let me call it free evaluation of evidence and the parties, and in particular the patentee, who is*

the one claiming that the priority right was transferred to a successor or the successor is then claiming that….[T]*he Boards of Appeal sometimes… use…sentences like, 'beyond reasonable doubt' or 'on the balance of probability'. And although this might be helpful in a certain case for a board my argument was always it is the Board or Court which has to be convinced by the evidence on file.*"

384. I must admit that I did not see the relevance of this line of questioning. These are civil proceedings brought in Ireland under Section 25 of the Patents Act 1992, as amended, and the standard of proof to be met in this jurisdiction is the balance of probabilities. The threshold to be met in this jurisdiction has been identified in numerous cases, most notably perhaps in *Banco Ambrosiano*. *SpA* v. *Ansbacher & Co. Ltd* (Unreported, Supreme Court, 8th April 1987). There Henchy J., at 84, makes clear that "*The normal rule in a civil case is that the person on whom lies the onus of proving a particular averment is held to have discharged that onus if the court is satisfied on the balance of probabilities that the averment in question is correct*". He went on to reject the proposition that civil cases involving fraud are an exception to that rule and that proof of fraud in such case requires a higher degree of proof than is normally required in a civil case. So it is entirely clear that the present case, which is far removed from a case of fraud (and even a civil case involving fraud would, as Henchy J. identifies, fall to be decided on the balance of probabilities) falls undoubtedly to be decided on the balance of probabilities.

3. Timing of Transfer to Successor

385. Asked by counsel for Teva whether a transfer must have occurred before a patent application is made, Dr Kinkeldey indicated as follows:

"[I]*n my view, and that is a very strong view I have, that transpires from the wording of Article 87(1) as such, saying that a person who has filed a first priority application and then files the second application, that that means in the moment, when the second application is filed, then it has to be a situation that he is either applicant and it's no problem or he's successor. And that transpires from the law. And that is followed by the Board. There is almost unanimous view on this at least in the Boards of Appeal. I know of one German…*[commentator]*…and he is of a different opinion. But that's the overwhelming opinion is that it has to be at the moment when the second application is filed. It must be sure who is the successor*."

4. Implied Transfer

386. Asked by counsel for Teva about the potential of the European Patent Office recognising an implied transfer (pre-patent application), Dr Kinkeldey indicated as follows:

"[T]*hat then goes into the direction of free evaluation of facts and evidence…. If there is, for example, an oral agreement but then we need some kind of witness or something which can convince us. And here the Boards, I think, go along with those means for proving something which are mentioned in Article 117 of the European Patent Convention….*[T]*he standard is to convince the deciding body and of course you need material with which you could work and look at and then say this convinces me and that the other thing is not so convincing.*"

5. Role of National Law

387. Asked by counsel for Teva as to the role of national law in the evaluation of a supposed implied transfer, Dr Kinkeldey indicated as follows:

"[I]*f then I have, as a Board or Court to get to a fair and good answer, whether or not the succession in title has taken place, then normally the transfer of the priority right*

was done in the first country and, therefore, it's absolutely reasonable to rule, and that also has been done in many decisions now, that one looks to the national law of that country and has a look or gets information, hopefully: What was the rule in this very country?"

6. *Nunc Pro Tunc* Assignments

388. Asked by counsel for Teva if *nunc pro tunc* assignments are recognised by the EPO, Dr Kinkeldey observed that "*It's… a case to case thing to judge on this….*[T]*hat depends very much on the facts of a particular case….*[T]*hat is a very, very much case bound situation.*" (A *nunc pro tunc* assignment is an assignment that is signed on one day but in which the parties agree the assignment to have taken place on some earlier date.)

7. Priority Right Based on Equity

389. Asked by counsel for Teva about the possibility of a priority right based on equitable title, Dr Kinkeldey observed as follows:

"*Well, of course we are now entering the dispute between Mr. Rennie Smith and myself about the decision J19/86* [in fact Case J-0019/87 *Assignee*].

[In that case, the applicant for a European patent had previously been advised that the assignment to him of the invention and the United Kingdom priority patent application had no legal effect because he had not signed it. However, according to the reasoned expert opinion of an English patent barrister, which the Board accepted as correctly representing relevant English law, the assignment did have the legal effect that the applicant became the owner of the invention and entitled in equity (*i.e.,* he had an equitable title) to the United Kingdom application. He was entitled to apply for and be granted a European patent in respect of the invention the subject of the United Kingdom application and also, for the purpose of filing the European patent application, a right of priority.]

May I say as a starting point, there is nothing wrong with this decision….[I]*t used something …similar to equitable…but the facts of this case were, insofar as were such that there was an agreement, an assignment, the assignment was already registered. The only thing which was missing was a signature and then there was a statement or an affidavit of a barrister in that case from the UK, convincing the Board that in the UK this would be a perfect case of an equitable right or transfer of rights. And I fully agree. I mean this is fair and is a decision which I wouldn't -- I'm quite happy with the decision. What I do not like is that one extrapolates from this decision a general philosophy that in each and every case an equitable right would be applicable. That, I think, would be wrong.*"

8. Proving Equitable Transfer

390. Asked by counsel for Teva what type of proof would be required at EPO-level to establish an equitable transfer, Dr Kinkeldey observed as follows:

"*Well, no difference as for a legal transfer right. Same proof. And I think there is one* [case]*...1786/15* [i.e. the *General Hospital* case]. *That is … as the most recent decision I digged … out dealing with this equitable right and with this decision 19/86* [in fact Case 19/87]. *And, I think, this decision is a very good decision in dealing with it. And they, well they tried to avoid in a way to criticise decision 19/86, other decisions did as well. And but here they said it doesn't matter whether it's a legal right or an*

equitable right, the question or what counts is that the evidence we have on file is not good in either aspect."

9. Transfers in Context Presenting

391. Asked by counsel for Teva whether she saw a transfer to have been effected in the priority year, to compare this with the situation in 2007, and the preferred identify of the party to file their patent application, the following exchange occurred between counsel for Teva and Dr Kinkeldey:

Counsel:	...[H]*ave you, on your review of the documents, identified anything that would constitute a transfer within the priority year?...*
Dr Kinkeldey:	*Not a single one…*
Counsel:	*Dr. Kinkeldey, I believe you've reviewed an assignment, a later assignment in 2007?....*[I]*f that assignment had been dated much earlier, would that be sufficient proof?…*
Dr Kinkeldey:	*Perfect. Had it been produced before...the second application was filed we wouldn't be sitting here.*
Counsel:	*And, equally, Dr. Kinkeldey, had the PCT application been filed in the name of BMS Pharma, as opposed to BMS Company, would there be any difficulty, in your experience, with priority?*
Dr Kinkeldey:	*I'm not sure whether I understood your question. I mean, it was filed. The first application was filed in the name… BMS Pharma and the second was filed in the name of BMS Company. And the question, of course, that would jump on me if I had the case on the table and had to decide that, prima facie I would say these are two different firms. And then I need some evidence on file, how the priority right was transferred from Pharma to Company*.

B. Cross- Examination

1. Dr Kinkeldey's Standing Within the EPO Boards of Appeal

392. A scientist who has also practised as a patent attorney, Dr Kinkeldey confirmed that she was a technical member of the Boards of Appeal.

2. Need for Agreement/Assignment under Article 87/EPC

393. Dr Kinkeldey confirmed her view that Art.87/EPC requires in effect that there must be proof that a person is a successor in title stating that:

"[T]*his, in my view, transpires in terms of linguistic and logic from this article that at the moment when the second application is filed, and it is named or there is the definition of successor, then there must be something…which proves that he's a successor.*"

394. Moving on, Dr Kinkeldey accepted the proposition that:

(i) the question of succession in title is governed by national law.
(ii) the formal requirements applicable when one transfers a patent or patent application do not apply to a right of priority *i.e.* one cannot reject an assignment of a priority right on the basis that it does not satisfy formalities.
(iii) while the Boards of Appeal are still reaching for a "*possibily harmonised view of how high the standard of proof has to be before the Boards of Appeal*", in this case the standard of proof is the standard applicable in Ireland (*i.e.* on the balance of probabilities).

(iv) (in the context of Case T-0577/11 (*Entitlement to priority*) (considered later below)) (a) Art. 87 EPC requires neither an express assignment in writing, nor excludes a transfer by operation of law or by implied contract, and (b) succession in title needs to be considered in the context of a comprehensive system of law (agreeing with the proposition of counsel that "*The EPC is a patent code; it cannot give the full system of law*").

(v) having been asked to reconcile her acceptance of point (iv)(a) above and her previous assertion that an assignment is necessary, Dr Kinkeldey stated:

> "*That is perhaps now a question of interpretation of the word 'assignment'. I mean, I'm not a mother tongue in English, as everybody knows....and when talking about an assignment, I read it that something has -- there has to be an agreement and....maybe I'm a little bit influenced by...German law thinking and we were educated in civil law and I have become a German patent attorney and that means that there have to be two parties; the one parties offer something and the other one accepts that. That is then the contract. And something of this kind and I would call it an assignment, a transfer of a right or whatever; I give something away, somebody offers to give something away and the other party accept that. And only then, according to German civil law, this would then be a contract which would be valid. And I interpreted the word 'assignment' in this way. And I think that that has to happen here. No matter how this transfer or assignment then later can be proved, let's say before a court, when it comes to a conflict, and it is necessary to prove it, if I have a written assignment, no question, then it's easy thing. But if I don't have that, that doesn't rule out other means, how this contract or this exchange of something here in exchange of the right to priority has happened….And that is what I understand with 'assignment'; it's not necessarily a written assignment or written agreement, it must have taken place… before the subsequent application was filed.*"

3. Priority on the Basis of Equitable Ownership

395. Turning next to the issue of priority on the basis of equitable ownership, having been led by counsel for BMS through a number of decisions of the EPO, namely:

– Case T-0577/11 (*Entitlement to priority*) (ECLI:EP:BA:2016:T057711.20160414). There, an argument was made that there was an economic right under Dutch law, and ultimately the Board of Appeal rejected it. What is significant about the case is that the Technical Board of Appeal essentially crystallised what it is about beneficial ownership that makes it a satisfactory basis upon which to assert priority. The essence of the decision was the distinction that the Board drew between the equitable ownership that presented in J-19/87 and the economic interest asserted under Dutch law whereby there was no power in the owner of the economic interest to require the legal interest to be assigned to it. In its decision the Technical Board of Appeal observed, amongst other matters, as follows:

> "*The formal defects in the assignment could have been remedied by the contracting parties at any moment after its conclusion, and this remedy was legally possible under English*

law. In the present case, the parties contractually agreed that the assignment agreement, which was concluded after the filing date of the subsequent application should have retroactive effect in relation to the transfer of economic ownership only. It was not intended that the legal title too should be transferred as from the earlier date, nor could it have been acquired."

As can be seen, what the Board is setting out and crystallising in the just-quoted text is that the essence of equitable or beneficial ownership that allows it to be a satisfactory basis upon which to claim priority is that the owner of the beneficial interest has the right to call for the legal interest, so it has a right to protect its title. In the present case that, of course, assumes particular significance because it does not seem to be disputed that BMS Co did have a right to call for the legal assignment to it of US 165.

– Case J-19/87 *Assignee* (ECLI:EP:BA:1988:J001987.19880321). There, the applicant for a European patent had previously been advised that the assignment to him of the invention and the United Kingdom priority patent application had no legal effect because he had not signed it. However, according to the reasoned expert opinion of an English patent barrister, which the Board accepted as correctly representing relevant English law, the assignment did have the legal effect that the applicant became the owner of the invention and entitled in equity (*i.e.,* he had an equitable title) to the United Kingdom application. He was entitled to apply for and be granted a European patent in respect of the invention the subject of the United Kingdom application and also, for the purpose of filing the European patent application, a right of priority.

and

– Case T-1103/15 *University of Alabama* (ECLI:EP:BA:2018:T110315.20180222). There, the opposition division of the European Patent Office arrived at the conclusion that: (i) the priority of US 326704 P of 3rd October 2001 was not valid; (ii) D3, a document published on 17th April 2002, before the filing date of the patent in suit (3rd October 2002) was therefore a document according to Article 54(2) of the European Patent Convention for the claimed subject-matter and its content anticipated claims 1 and 5 of the main request. In the statement of grounds of appeal the appellant did not contest that the main request lacked novelty over D3. The question that the Board had to answer was rather whether the right of priority had been validly claimed to determine whether D3 was a document or not according to Article 54(2) of the European Patent Convention. The appellant had contended that the question whether the right to claim priority had been validly acquired by the applicant of the subsequent application was a matter of national law. However, in its decision, the Technical Board of Appeal noted as follows, at §§1.6-1.7:

"*1.6* [T]*he main evidence the appellant has submitted to support its view is an extract of a judgment from a UK court in which the court found that under English law a priority was validly claimed in the UK, having regard to US federal and the law of the State of Georgia (D16...)...whereby the principles of US law had been agreed by the parties....One of the principles the parties had agreed upon was that*

Georgia law recognises the concept of equitable rights....

1.7 *In the view of the Board, D16 does not qualify as suitable evidence to prove the relevant provisions or recognised operations of US law, be it federal or state law. If US state law were applicable, the board assumes it would be the law of Alabama. Therefore there is no convincing evidence on file to prove the appellant's assertion that the University of Alabama is successor in title to the applicants of the earlier application.*"

Dr Kinkeldey indicated that when it comes to succession of title on the basis of equitable title "*if national law allows it, and that is the decision J 19/86* [in fact, Case J-19/87] *, the equitable title is apparently all right*."

396. Counsel for BMS then put a number of propositions to Dr Kinkeldey by reference to the above-mentioned decisions of the EPO and whether or not she agreed with them. The following exchange occurred between counsel for BMS and Dr Kinkeldey at this juncture:

Counsel: *What I want to put to you, having gone through those cases; first of all, that there are actually EPC decisions that either give effect to an equitable title or envisage giving effect to an equitable title. And the key is the applicable law. You'd agree with that?*

Dr Kinkeldey: *Yeah.*

Counsel: *Thank you. Secondly, the principle that national law governs the situation is actually a very strong principle?*

Dr Kinkeldey: *Yeah.*

Counsel: *And under T-205/14* [*Ibandronate sodium, Form QQ/Teva* (ECLI:EP:BA:2015:T020514.20150618)]*, it's the entire system of national law that comes into play?*

Dr Kinkeldey: *Yeah….*

[In that case, it will be recalled, the appellants contested the entitlement of the patent in suit to the priorities from US applications Nos 60/604, 026 of 23rd August 2004 (P1) and 60/690,867 of 16th June 2005 (P2). They argued that the respondent had failed to prove to the required standard that, on the date of filing of the international application number PCT/US2005/030500, published as WO 2006/024024, the rights of priority derived from the US provisional applications (P1) and (P2), both filed in the name of the three inventors, had been validly transferred to the respondent. As a consequence, the date of filing of the international application WO 2006/024024 was the effective date for determination of the relevant state of the art. In the course of its judgment, the Technical Board of Appeal, amongst other matters, observed at §3.6.3 that "*Since the provisions of the EPC do not lend themselves to an autonomous determination of the requirements for the transfer of the right of priority, the validity of such transfer is a* ***matter of national law****.*" [Emphasis in original].]

Counsel: *And that would, therefore, include the equitable principles in national law?*

Dr Kinkeldey: [Witness Nods].

Counsel:	*You accept that....And...coming back again, tying back into your report, there's actually no limitation imposed by the EPC that you need an assignment, it's for national law?*
Dr Kinkeldey:	*Yeah....*
Counsel:	*....So, you've agreed that an assignment is not required if the applicable law does not require that?*
Dr Kinkeldey:	*Mm hmm.*
Counsel:	*And if ownership passes?*
Dr Kinkeldey:	*Mm hmm.*

397. One slightly peculiar feature of Teva's written closing submissions is that it seems to proceed on the basis that Dr Kinkeldey did not give the evidence that she provides in the last-quoted exchange between her and counsel for BMS. One would imagine from those closing submissions that Dr Kinkeldey's evidence remained as initially proffered, *i.e.* that (i) Art.87 requires some sort of agreement and (ii) that there is a very restricted scope within which to accept equitable ownership of a priority document as a basis on which to claim priority. However, these are two things that Dr Kinkeldey clearly and comprehensively resiles from in the last-quoted exchange between her and counsel for BMS.

398. In truth, in that exchange Dr Kinkeldey essentially agrees with the evidence that was put in originally by Mr. Rennie-Smith, offering conclusions that are inescapable when one has regard to the applicable case-law of the European Patent Office (which was also touched upon by counsel for BMS in her cross-examination of Dr Kinkeldey and which I have considered). The two points that arise from those cases, it seems to me can be shortly put: (1) the only thing that can be derived from Art.87 of the European Patent Convention is that the person who says 'I am the successor in title' must own the priority right at the relevant time, *i,e.* at the time of the subsequent application; (2) once that is in place, the question as to whether they do own the priority right is a matter for national law.

C. Re-Examination

1. Application of National Law

399. Counsel for Teva brought Dr Kinkeldey to the decision of the Board of Appeal in Case T-1201/14 *(Transfer of right of priority)*. There, it will be recalled, the patent proprietor was Innovative Sonic Ltd. It claimed priority from a US provisional application. The US provisional application was filed by the inventor and assigned to ASUSTeK. Innovative Sonic claimed that there had been a transfer from ASUSTeK by reason of: (a) a *nunc pro tunc* assignment under US law; (b) an implied transfer under either German or Taiwanese law; (c) a direct transfer under US law. In respect of (b) Innovative Sonic on a general policy as to the transfer of new and pending patents between it and ASUSTeK and certain instructions to patent attorneys. The following exchange occurred between counsel and Dr Kinkeldey:

Counsel:	...[C]*an I just ask you one question based on that material, Dr Kinkeldey. While you agree that national law applies, would you agree that it is an open question as to the choice of different national laws that may apply in a given case?*
Dr Kinkeldey:	*Well, doesn't that depend on the case and on the parties involved and which law has to now be looked at? I would say if there is a conflict between two US firms, I wouldn't apply a German law, for example to make an extreme example*.

2. Transfer vs Assignment

400. Counsel queried whether Dr Kinkeldey intended any difference when she used the term 'transfer' or 'assignment'. To this, Dr Kinkeldey indicated as follows:

> "*No, that is my point I think I interpret the words 'agreement', 'assignment' and 'transfer of right', although transfer of right has to be taken on an agreement or an assignment, not necessarily in written form, but just two parties have to agree to transfer the right of priority. And to me, the word 'assignment' covers this.*"

3. Being a Technical Member

401. Having confirmed that she had been a technical member of the Boards of Appeal, Dr Kinkeldey elaborated as follows:

> "*I want to say I am very grateful when the legally qualified member assists me in finding the decisions. And of course there is no difference, it is just when a case comes in, I have a look into the case and I see where the core issues lie and then I either appoint the technically qualified member as rapporteur and if and when it comes, for example, to inventive step, which is normally a purely technical issue or if there is a legal issue like the right of priority…a legally qualified member….And then …the Board rapporteur…will write about it. And then the whole Board is then thinking and sitting on the question and deciding in total in deliberation….And my position as Chair is, of course, then to understand everything and bring everything under one hat.*"

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The Evidence of Mr Rennie-Smith

A. Introduction

402. Mr Rennie Smith holds a first class law degree from Cambridge University, has practised as a solicitor and, most pertinently for the purposes of the present proceedings, is a former member of the Boards of Appeal of the European Patent Office, having served as a legally qualified member of the Enlarged Board of Appeal from 2005 and been chairman of the Technical Board of Appeal from 2010. Subject to para.4 of this judgment, an abridged version of his reports is attached hereto as Appendix 11. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

403. In his first statement Mr Rennie Smith indicates as follows (at §7):

> "*I have been asked by McCann FitzGerald LLP, solicitors for the Respondent, BMS Ireland Unlimited Company...to act as independent expert in these proceedings on the question whether under the law and practice of the EPO the claim in European Patent EP1427415, of which BMSHIUC is the proprietor, to priority from the United States provisional patent application US 324165 would be considered valid*".

B. Examination

1. Article 87 EPC

404. After the usual preliminaries regarding Mr Rennie-Smith's witness statement being his own, *etc*., counsel for BMS noted that it is undisputed that Art.87 governs the right of priority and asked Mr Rennie-Smith to outline what, if anything, is to be drawn from Art.87 in relation to the question of how succession in title to the right of priority is to be established. To this, Mr Rennie-Smith responded as follows:

> "*Not a great deal. Article 87 simply says that either an applicant for an earlier case filed in the Paris Convention or World Trade Organisation country can obtain the benefit of priority by, if he applies within a year for a European patent and then there is the alternative that this could be not the earlier applicant, but the earlier applicant's successor in title. So the main limitations in Article 87 are that there must be a succession and it must be within the year.*"

405. Mr Rennie-Smith further confirmed that Art.87 does not state how succession in title is to be determined.

406. Counsel for BMS also brought Mr Rennie-Smith to T 1201/14 – 3.5.05 [p.337 of the Book of Authorities, p. 23 of the judgment] where the Board of Appeal states as follows, at para. 3.1.1.3:

> "*Hence, the substantive requirements derivable from the EPC for a valid transfer of the right of priority may be summarised as follows:*
> *The successor in title with respect to the right to claim priority from a first application according to Article 87(1) EPC 1973 must prove that it indeed owned,*
> *(i) before the filing of the later European application,*
> *(ii) the right of priority relating to the first application for the purpose of filing the later European application claiming that priority."*

and had Mr Rennie-Smith confirm that (i) what the Board of Appeal was stating was that (a) the successor in title owns a right to claim priority before the filing date of a later application, the European application, (b) ownership by right of succession has to be proved and done within a year, and (ii) this is a fair statement of what the Boards of Appeal draw from Art.87 generally.

2. Succession in Title and National Law

407. Asked to confirm that his evidence is that in the absence of provision for how succession in title is to be determined in the EPC itself, EPO decision makers essentially conduct the assessment by reference to national law, Mr Rennie-Smith confirmed that this was so.

408. Counsel for BMS brought Mr Rennie-Smith to T 0205/14 [p.163 of the Book of Authorities, p 29 of the judgment] where the Board of Appeal states as follows, at para. 3.6.2:

> "*The board further considered the question whether the silence of the EPC with respect to the requirements for a valid transfer of a right of priority implies that there are no formal requirements for such a transfer under the EPC. It would thus be possible to establish a transfer of a right of priority using any kind of evidence within the meaning of Article 117 EPC. It would be sufficient to demonstrate such a transfer by way of conduct of parties to a contract implying the transfer in the circumstances of the case. However, this would exclude the possibility of a transfer by operation of law which can only be established by reference to a (comprehensive) legal system. Also, the board's assessment of the evidence adduced will inevitably need to be made by reference to defined formal and material requirements. As an example, the question whether it is sufficient to have a declaration by the transferor only or whether an employee may transfer all its future rights in an invention to an employer cannot be resolved under the EPC. It has to be born in mind that the EPC does not establish a full harmonised patent system, although a high degree of harmonisation between the EPC and national laws has indeed been achieved. Neither the interpretation of the EPC nor the application of Article 125 EPC, which refers to procedural law only, constitute a proper basis for further harmonisation to the extent that the EPC does not clearly provide for harmonised law itself. For these reasons, the board did not take silence as a conscious choice of the legislator that the transfer of a right of priority is free of requirements as to form and content."*

and asked Mr Rennie-Smith comment on what the Board is stating in the just-quoted text. To this, Mr Rennie-Smith responded as follows:

> "*The Board is pointing out that the EPC...does not provide everything required to establish whether there has been a transfer, the right to claim priority. For example, it says you might be able to demonstrate a transfer by conduct of parties to a contract, however that would include a possibility of transfer by operation of law. It's basically saying the EPC is not a sufficiently developed system of law. It's what my professor of jurisprudence would've called an immature legal system I think. So you have to look elsewhere...And so it says...there is some harmonisation between the EPC and national law and you need to go further. It's concluding by saying it doesn't take the silence of a conscious choice, that the transfer of priority is free from requirement. So you have to go somewhere to find what those requirements are.*"

409. Asked if the foregoing accords with his experience and knowledge of how decisionmakers in the EPO approach the question of establishing succession in title, Mr Rennie-Smith responded in the affirmative.

410. The following exchange then occurred between counsel for BMS and Mr Rennie-Smith:

Counsel: ...[I]*f ownership of the priority right is established under national law, does the EPC or do the EPO decision makers apply any additional requirement over national law to the question of succession in title?*

Mr Rennie-Smith: *No, the basic principle is you decide what national law applies and then – which is a matter of evidence, obviously you can't know all the national laws, and then having established what national law, you see whether you're satisfied that, according to the criteria of that law, there has been a transfer....*

Counsel: *Is an assignment ever required if the applicable national law does not require it..?*

Mr Rennie-Smith: *....No, there's no requirement, as such, for an assignment. If, hypothetically a national law said the only possible way would be by some particular formality, then that would have to be demonstrated.*

Counsel: ....[I]*s equitable ownership of the right to priority ever rejected by...EPO decision makers if it would be sufficient under the applicant national law?*

Mr Rennie-Smith: *There have been examples of where it's been argued and it's been rejected. There's no reason why, if it was allowable under a national legal system and demonstrated to have taken effect under those criteria of that system then that would be acceptable.*

Counsel: *....I wonder could you...comment...generally, on how the question of equitable title to the priority application has been dealt with by the Boards of Appeal and perhaps by the EPO generally, just making references to the authorities that you are aware of in this regard?*

Mr Rennie-Smith: *...I hope I'm not repeating myself now, but where equitable interest – equitable title, rather, is demonstrated according to what is accepted as the national law to be applied, then it's been accepted - well, I can think offhand of -- you mentioned already the case, you didn't name it, but the case where there was a defect in an assignment document which hadn't been signed. That's J 19/87* [*Assignee*]*....There's examples where...the EPO has accepted or been prepared to accept equitable rights arising from employment contracts. You might say that there would need to be some further affection of title, but the equity is there, the obligation is there....I can* [also] *think of examples where it hasn't happened and that is where somebody tried to say that a particular form of ownership under Dutch law was the same as an equitable title in English or American or Irish law. And the Board there said; well, the cases which say you can do it under the English or Irish or American law are okay, but we're not going to accept that this Dutch system is the same.*

Counsel: *....I think the case you are referring to there...is case T577/11* [*Entitlement to priority*]*?*

Mr Rennie-Smith: *....Yes.*

Counsel: ...[C]*an you just give...your view of...the importance of that case in terms of equitable title? ....*

Mr Rennie-Smith: ...[T]*hat decision says expressly that an earlier case – and that is the J19/87* [*Assignee*] case *– was on its facts correctly*

decided. That in that case English law had been applied and English law allowed equitable title and that was acceptable. So, it confirmed the earlier decision, if you like....Then...it dismissed the argument that, in that case...what was called economic ownership under the law of the Netherlands was somehow akin or the same as equitable title in the common law countries.

Counsel: [turning to Case T0590/98 *Radiopharmaceuticals/AMERSHAM PLC* (ECLI:EP:BA:2003:T059098.20030430).

Respectfully, I do not see the relevance of this case to the case at hand. Case T0590/98 concerned the question of whether BMS Pharma could appeal a decision from an opposition commenced in the name of the DuPont Merck Pharmaceutical Company. So, just to note, it did not, *e.g.*, concern the issue of whether BMS Co had a beneficial interest in the intellectual property of BMS Pharma as a matter of Delaware law. The materials supplied to the Technical Board of Appeal in that case were clearly understood by the Board to establish that BMS Pharma Co was one and the same entity as the previously named DuPont Merck Pharmaceuticals company. I cannot discern any relevance between this case and the matters now in issue before me as to priority.]

....So...far as I understand it, the issue in that case was whether Bristol-Myers Squibb Pharma Company was entitled to appeal an opposition that had been begun in the name the DuPont Merck Pharmaceutical Company....And in fact there was another name change in the middle, there was a different name then, DuPont Pharmaceuticals company....Can you just...inform the court what was the finding in that case? ....

Mr Rennie-Smith: *In this case, a patentee, which was obviously resisting the opposition to its patent, claimed, alleged that there had actually been a change of opponent, that the party which was now before the Board was not the party which had commenced the opposition and that this had taken place without any transfer of the opposition. There are limited circumstances under which an opposition may be, it may be accepted that an opposition has transferred from one party to another. A question which is also decided according to national law, by the way. And in this case, the patentee said...it's not the same party and what we did at the hearing...*[was] *we sent the parties away to file evidence on the issue, because it had come up at the hearing. And the evidence filed was to the effect that...it was all related to packaging which suggested the trademarks which were used were owned by a party which was not the party in question and so on. And the opponent filed evidence from both its in-house lawyer and its external legal adviser to say this has been a change of name, that it's been the same party throughout. And we accepted that evidence. And we didn't accept the evidence based on what was called the public*

	record, which was actually these trade marks and packaging and various other indicia rather than actual proof of any change. And we said, effectively, the person who knows his affairs best is the person who conducts them. They say they have been the same party throughout then we accept that.
Counsel:	*So, the finding was that the entity hadn't changed in fact?*
Mr Rennie-Smith:	*Correct....*
Counsel:	*Was the question of equitable title in any way relevant to that decision?*
Mr Rennie-Smith:	*I don't think it had anything do with it whatsoever.*

C. Cross-Examination

1. Case T0590/98

411. Counsel for Teva began her cross-examination of Mr Rennie-Smith by bringing him again to Case T0590/98 *Radiopharmaceuticals/AMERSHAM PLC*. Again, respectfully, I do not see the relevance of this case to the case at hand. Case T0590/98 concerned the question of whether BMS Pharma could appeal a decision from an opposition commenced in the name of the DuPont Merck Pharmaceutical Company. So, just to note, it did not, *e.g.*, concern the issue of whether BMS Co had a beneficial interest in the intellectual property of BMS Pharma as a matter of Delaware law. The materials supplied to the Technical Board of Appeal in that case were clearly understood by the Board to establish that BMS Pharma Co was one and the same entity as the previously named DuPont Merck Pharmaceuticals company. I cannot discern any relevance between this case and the matter now in issue before me, namely whether BMS Co had the beneficial interest in US 165 on 17 September 2002 when it applied to file WO652. In any event, asked whether:

(i) this decision considered whether the appellant continued to be the same party or a successor, Mr Rennie-Smith confirmed that this was so,

(ii) ultimately the Board in that case, of which Mr Rennie-Smith was a member, decided that the appellant continued to be the same party, so, therefore, the question of succession didn't arise, Mr Rennie-Smith indicated that this was so, that "*the patentee was using an alleged non-continuance*",

(iii) BMS was the opponent and the patentee was not BMS, Mr Rennie-Smith confirmed that this was so,

(iv) during the pendency of the appeal the entity had changed its name twice so that by the time the Board's decision was delivered, the entity's name was BMS Pharma, Mr Rennie-Smith indicated that he believed this was the case,

(v) (a) at paragraph 1 of the Board's decision the issue identified by it to have arisen was "*whether there had at all times during the appeal proceedings been an appellant which had been either a party adversely affected by the decision under appeal or the universal successor to such a party*", and (b) ultimately the Board decided the matter on the basis that the first limb of that test was satisfied (*i.e.* that there had been a continuity of identity), Mr Rennie-Smith confirmed that this was so,

(vi) in support of that finding the Board relied upon Delaware law, Mr Rennie-Smith confirmed that this was so,

(vii) the Board had relied on an opinion as to Delaware law, Mr Rennie-Smith confirmed that this was so

(viii) (a) among the Board's observations there is a finding that "*Since on the only evidence available to the Board the appellant has throughout remained the same entity, no question arises of any transfer to another party of the appellant's assets or of its status as opponent or appellant*", and (b) the Board meant by this that (I) the second limb of the test did not arise, (II) so there was no question of succession, (III) it was deciding the entitlement to

maintain the appeal on the ground that it was the same party, Mr Rennie-Smith responded:

> "*Yes, that's probably right. I wouldn't say test was the right word; we were simply summarising in the previous paragraph the question we had to decide....But, yes, the last sentence of the paragraph that comes over from the previous page is a summary of the decision. I would just point out...that the evidence of Delaware law had not been challenged, as such.....So the opinion that you have referred to and the other evidence I mentioned was, in effect, unchallenged...*[T]*he evidence from the other side was of a completely different character*."

(ix) the patentee/respondent in that case had relied on various marketing materials that were publicly available, Mr Rennie-Smith confirmed that this was so,

(x) the said marketing materials "*tended to indicate that the various marketing activities were being undertaken by, in the name of, let's say, another BMS entity...but ultimately the Board was not very convinced by that evidence*", Mr Rennie-Smith responded that "*I would have to look back and read it again to check on the exact name. But it certainly wasn't the same party as – well, the argument was, based on the evidence they produced, that it was a different company that was now marketing products than the previous one, which we didn't find impressive*",

(xi) the Board had regard to an affidavit of Dr Larsen, a patent attorney, Mr Rennie-Smith indicated that this was so,

(xii) he could explain the test of successor in business asset as referred to by Dr Larsen in his consideration of whether BMS Pharma Company was the successor in business assets to the original party, DuPont Merck Pharmaceuticals, Mr Rennie-Smith

(a) observed that: "[T]*he way of establishing an acceptable succession of one party to another so as to, in effect, substitute as an opponent, is to demonstrate that the opposition has been transferred from, let's say, A to B as part of transfer of the assets of the business – and this is the way it's put in the case law – in the interests of which the opposition was filed. That's a summary of the case law principle, if you like*",

(b) agreed when counsel put it to him that "[T]*here are two ways in which you can succeed as a legal entity, as opposed to a natural person, to opposition proceedings; one would be by being the same party or continuing to be the aggrieved party and the other way...is by being the successor of business assets*", and

(c) for completeness added "*that in the...pretty rare case where you have an individual, as opposed to a corporate opponent – well, I remember one case, it's actually referred to for other reasons in my report, an individual who died, then one was looking at whether there had been a succession. And there you don't need business assets, there it's a matter of whether or not*

that person...under the relevant law, inherits".

2. Documents/Facts Relied Upon – I

412. In response to further questions, Mr Rennie-Smith confirmed that: (i) the priority application, the patent, the inventor's assignment, the witness statement of Mr. Golian and the first witness statement of Mr. Chandler were the only documents he received at the time of drafting his first report, (ii) when he came to make his second statement in May 2022, he had by then received a copy of Dr. Kinkeldey's first report, possibly Mr Steele's report (he was unsure), possibly Prof. Thomas' report (he was unsure), (iii) he had not asked if there had been any further assignments of US 165. (Mr Rennie-Smith made mention of an assignment of 2002 at this time which caused a degree of confusion as to what document this was. This aspect of matters is dealt with in my consideration of the re-examination later below).

3. Mr Chandler's Evidence

413. Counsel noted that in his first report, Mr Rennie-Smith says that he sees "*no reason why the EPO would not accept Chancellor Chandler's expert evidence of Delaware law as demonstrating that BMS Company was the successor in title to the right to claim priority*", and also that "*In my opinion, on the facts of the present case, including the expert report of Chancellor Chandler, the EPO would, if required to decide the issue, accept that at the date of the PCT application BMS Co had an equitable title to claim priority.*" So, counsel summarised, "*you reach a conclusion, which is that the EPO would accept Chancellor Chandler's evidence and you see no reason why they wouldn't.*" Asked if that remained his evidence, Mr Rennie-Smith confirmed that it did.

414. Asked whether he had compared Mr Chandler's evidence to that of Mr Steele (both men gave evidence on Delaware law), the following exchange occurred between Mr Chandler and counsel:

Mr Rennie-Smith:	*It's a weighing up test, as you know; once you've ascertained the relevant law you have to decide what's demonstrated. Obviously, when you actually have opinions which are contrary to each other, you have to decide which is the more appropriate, which is the more convincing.*
Counsel:	*Did you undertake that exercise?*
Mr Rennie-Smith:	*No, I don't think I was asked to....*
Counsel:	*I'll take that as a no then, you haven't undertaken that exercise of comparing the expert evidence of federal and Delaware law on both sides; is that right?*
Mr Rennie-Smith:	*Yeah.*
Counsel:	...[D]*o you still maintain...there's no reason why the EPO wouldn't follow Chancellor Chandler's expert evidence?*
Mr Rennie-Smith:	*No...the EPO, if it was faced with this, would have to conduct the exercise I've described in my reports....*
Counsel:	*So, is there a reason why they wouldn't follow Chancellor Chandler's evidence then?*
Mr Rennie-Smith:	*If they were more convinced by other evidence, yes.*
Counsel:	*...But you don't allow for that possibility in either of your...reports?*
Mr Rennie-Smith:	...[W]*ell, the reports don't say that, yes, I agree.*

4. Documents/Facts Relied Upon – II

415. Counsel returned again to the issue of the facts on which Mr Rennie-Smith had based his

opinion. Asked:

(i) what facts he based his opinion on, Mr Rennie-Smith indicated that these are summarised in paragraph 11 of the report,
(ii) whether, since preparing these two reports in April and May of last year, he had learned any other facts about this case, Mr Rennie-Smith could not recall that he had,
(iii) whether he had received any further documentation other than the cross-examination materials that were furnished to him, Mr Rennie-Smith indicated that he had seen the Steele report and the Thomas report, a copy of a witness of fact statement from somebody at BMS (whose name he did not fully recall),
(iv) whether he had received an administrative training manual or a training manual at any stage, Mr Rennie-Smith indicated that he had not,
(v) whether he had received any e-mails from the first half of 2002, Mr Rennie-Smith indicated that he had not.

5. EPO View of Assignments

416. Counsel noted that Mr. Rennie-Smith, at para.21 of his first report, considers the inventor assignment of 3rd November 2001, and states, amongst other matters:

> "*The words of the document are so clear as to be unambiguous. I have no doubt that, if required to consider the document, the EPO would find that it had the effect, as of 3 November 2001, of making BMS Pharma the successor in title to the priority right of the two inventors.*"

417. Asked why he had reached this conclusion, Mr Rennie-Smith indicated that this was because "*it* [the assignment] *was quite clear; it included the priority rights.*"

418. Counsel noted that in his second report Mr Rennie-Smith states that it is easy to establish succession in title when there is an agreement which proves the transfer, Mr Rennie-Smith responded that "*The EPO is fond of documents....It's much happier to work with documents than with any other form of evidence.*"

419. Counsel then brought Mr Rennie-Smith to the assignment of April 2007 and asked whether, "[i]*f you saw this assignment, as a member of the Board of Appeal, would that likewise be an easy case where the words of the document are so clear as to be unambiguous?*", Mr Rennie-Smith responded "*It's straightforward, I agree. If you saw the two together, you might think twice.*"

6. *Innovative Sonic*

420. Counsel turned next to the *Innovative Sonic* case, *i.e.* Case T-1201/14 *(Transfer of right of priority)*. There, it will be recalled, the patent proprietor was Innovative Sonic Ltd. So the case is generally known as the *Innovative Sonic* case. Innovative Sonic claimed priority from a US provisional application. The US provisional application was filed by the inventor and assigned to ASUSTeK. Innovative Sonic claimed that there had been a transfer from ASUSTeK by reason of: (a) a *nunc pro tunc* assignment under US law; (b) an implied transfer under either German or Taiwanese law; (c) a direct transfer under US law. In respect of (b) Innovative Sonic had a general policy as to the transfer of new and pending patents between it and ASUSTeK and certain instructions to patent attorneys. The Technical Board of Appeal found that Innovative Sonic had not proven succession in title. In so holding, the Technical Board of Appeal emphasised that the policy and instructions had not been consistently followed. However, as mentioned previously above, a critical difference between that case and this is that (as the Technical Board of Appeal notes in its consideration of the proposition that there had been a transfer by virtue of a general

policy under German law) Innovative Sonic submitted that "*By executing...policy the right of priority for the patent in suit was transferred to the appellant*" (§3.2.2). Here, BMS has never sought to rely on a policy as yielding a transfer of a priority right. Its case has been one of control, namely that the making of policy as regards intellectual property within BMS Pharma was but a manifestation of the control that BMS Co enjoyed under Delaware law and, by operation of the law of that jurisdiction, BMS Co was the beneficial owner of US165.

421. The following exchange took place between counsel and Mr Rennie-Smith:

[I. Facts]

Counsel: ...[I]*n that case...the patentee was an entity called Innovative Sonic Limited and it claimed priority from a US application which had been filed by the inventor and then assigned to an entity called ASUSTek. And Innovative Sonic claimed that there had been a transfer from ASUSTek by reason of three different things: First, a nunc pro tunc assignment under US law; second, an implied transfer under either German or Taiwanese law; and third, a direct transfer under US law. And you cite this in your first report, I think, as an example where the EPO has to grapple with multiple different options when it comes to national law, isn't that right?*

Mr Rennie-Smith: *Yeah.*

[II. Similarities with Present Case]

Counsel: ...[D]*id you consider any similarities between this case and BMS's claim to priority?*

Mr Rennie-Smith: *No, not really. This is a case where...the EPO – I use 'the EPO' to mean – ...all levels of the EPO - has, first of all, to struggle with problems to decide what the appropriate national law is....*[I]*n some cases, it's clear what the national law is....In this case, this Board had to deal with...four arguments based on three different candidates for national law....*

[III. Delaware Law]

Counsel: ...[W]*e don't need to decide which is the appropriate outcome, but I just wanted to illustrate how complex the choice of law can be....Now, in your report you say that the choice of law in this case is straightforward; it's Delaware law..?*

Mr Rennie-Smith: *On the evidence I had when I made my report, yes.*

Counsel: *Do you maintain it's straightforward now...?*

Mr Rennie-Smith: *Personally, even knowing what I know now, I think probably the EPO would decide Delaware law....*

[IV. Outcome]

Counsel: *....And in this case, before we come to the facts, isn't it the case that the Court decided that it would be the same outcome, regardless of what national law applied..?*

Mr Rennie-Smith: *I would have to re-read the text of this decision. But it*

doesn't surprise me. As I recall, they didn't find a transfer on any of the routes under any of the candidate laws, so...

[V. Standard of Proof]

Counsel: *That's right. And does that sometimes happen; where the requisite standard of proof, however described, is not met, the Board doesn't go down into the weeds of national law if it's content that the evidence simply isn't adequate –*

Mr Rennie-Smith: *....If somebody's got to make four arguments based on three candidate national laws, it's obvious that it's not very clear what the appropriate national law is. And one suspects – of course you don't know unless you've actually seised of the case yourself – one suspects that it's a slightly weaker case than if it was just one candidate.*

Counsel: ...[O]*ne of the arguments...that was made in this case was that there had been an implicit transfer of the priority right under German law. And I'll ask you to just turn to...paragraph 3.2.2* [which states]:

> "*The appellant submitted that a general policy had been established between ASUSTeK*" - that was the priority rights holder – "*and itself and had been followed by both parties*,"

and....over the page...the policy is laid out there:

> *"Beginning from the end of 2006 intellectual property in the field of telecommunications standards should be transferred from ASUSTeK to Innovative... since Innovative was founded as a trust holder for ASUSTeK. All pending applications and granted patents in this field with the exception of six particular cases that ASUSTeK wants to keep should be transferred to Innovative"*

...[a]*nd then a little bit further down:*

> *"New cases should also be transferred to Innovative and ASUSTek."*

....[D]*o you remember what the Board had to say about that policy?*

Mr Rennie-Smith: *...I think they said that they were unconvinced that that was sufficient to transfer.*

Counsel: *...You're absolutely right....*[a]*nd before we get to the Board's reasons, you'll see...at...*[para.] *3.2.2.2, the Board identifies the burden of proof, which...rests with the person claiming priority, isn't that right?*

Mr Rennie-Smith: *Yes.*

Counsel: *And then it identifies the standard of proof being beyond reasonable doubt in these particular circumstances..." ...because practically all the evidence regarding the general policy lies within the knowledge and power of only one party to these inter partes proceedings..." And a case is*

	cited....[D]*o you agree that that's the appropriate standard to apply in those particular circumstances where a party relies on a policy which is exclusively within its knowledge?*
Mr Rennie-Smith:	*No, not entirely. This is probably an undecided issue in this area of case law....*[T]*here are different views in the case law...on priority, as to whether it's balance of convenience or beyond reasonable doubt.*
Counsel:	*I don't disagree with you that different cases go in different directions. But in this particular case, do you agree with the reasoning that where practically all the evidence regarding the general policy lies within the knowledge and power of only one party to these inter partes proceedings, the appropriate standard is beyond reasonable doubt?*
Mr Rennie-Smith:	*No, I don't.*
Counsel:	*You say it's undecided, is that right?*
Mr Rennie-Smith:	*Yes....Laterally, there have probably been a few more cases than previously. But I mean, this is – when are we talking about here – this is 2017....*

422. Counsel turned next to certain findings of the Board:

– at §3.2.2.5 the Board states:

> "*Even in respect of 'new cases', the Board is not convinced that the above filing policy had always been complied with.*"

– at §3.2.2.5 the Board further states:

> "*Even assuming that such instructions did exist, it is apparent to the board that they were not necessarily followed by the employees of both companies in every case.*"

– at §3.2.2.7 the Board states:

> "*However, the board finds that the mere fact that patent attorneys receive instructions from companies to file patent applications does not automatically demonstrate that the right to claim priority from a first application was already validly transferred between the parties to the transfer before the filing date of the later application.*"

423. Asked if he was familiar with any instructions to patent attorneys in the present case, Mr Rennie-Smith indicated that he was not.

424. Counsel then turned to certain further observations of the Board:

– at §3.2.2.9, the Board refers to the fact that the alleged general policy was not consistently respected by the employees of both companies, then continues:

> "*Even assuming that the applicable national law did not prescribe that a transfer of the right of priority must be in writing and thus allowed for an implicit transfer, the appellant failed to sufficiently prove that the right of priority was validly transferred to it in an implicit way by virtue and in execution of a general policy between* [the priority holder] *and it.*"

425. Counsel then asked whether Mr Rennie-Smith saw any parallels between the facts of that case and the present case. To this, Mr Rennie-Smith responded:

> "*No, not really. Many different candidate national laws, the evidence appears to have been very disparate and inconsistent – I mean, I'm now going on what the Board says in its decision, because, of course, I don't know anything about the case beyond what you, as well as I, can read. I'm aware that in this case it is suggested that there is a policy which has been followed and that word is used in this case as well. But I think to say that's a parallel I would draw would be an exaggeration.*"

7. Case T1786/15 *General Hospital Corporation*
(ECLI:EP:BA:2020:T178615.20201015)

426. Counsel referred next to the *General Hospital Corporation* case. There, it will be recalled, the patent proprietor was the General Hospital Corporation and the employee-inventors were the applicants for the provisional application from which the patent claimed priority. The General Hospital Corporation filed the Patent Cooperation Treaty application. The inventors were required by D31 (MGH Intellectual Property Policy) to transfer certain IP rights to the Massachusetts General Hospital, the parent company of the General Hospital Corporation. The General Hospital Corporation relied on an internal 'Ownership reallocation policy' (D51) to assert a transfer of priority or equitable title from the parent (the Massachusetts General Hospital) to the subsidiary (the General Hospital Corporation) prior to the Patent Cooperation Treaty application. The Technical Board of Appeal found that the policy did not discharge the burden of proof because it did not provide evidence that it was in fact adopted. Notably, the General Hospital Corporation relied on an internal 'Ownership reallocation policy' (D51) to assert a transfer of priority or equitable title from the parent (the Massachusetts General Hospital) to the subsidiary (the General Hospital Corporation) prior to the Patent Cooperation Treaty application. As I have stated previously, BMS has never sought to rely on a policy as yielding a transfer of a priority right. Its case in this regard comprised the Control Proposition.

427. Counsel posited the *General Hospital Corporation* case "*also relied on a policy*". This led eventually to the following exchange between Mr Rennie-Smith and counsel:

Counsel: I'd just ask you to agree with me or not agree with me...[that] in that case the priority right was not established, because...the patentee could not provide conclusive evidence that the reallocation policy set out therein was in fact adopted..? I'm reading from the finding at paragraph 14 of the decision.

[Paragraph 14 states as follows:

> "*The board notes that document D51 is the key piece of evidence that purports to demonstrate that the right to claim priority from document D1 had been transferred to the appellant. However, in the board's judgment, Document D51 does not demonstrate to the required standard of proof that a reallocation of priority rights, had taken place by the filing date of document D2, 16 February 2006. This is because document D51 is unsigned and therefore it cannot provide conclusive*

evidence that the reallocation policy, set out therein, was in fact adopted."]

....So, can I ask you to agree with me then that where a patentee relies on a policy as proof of its title to a priority interest, the Board will have regard to whether that policy is implemented, as in *General Hospital*, isn't that right?

Mr Rennie-Smith: Yes.

Counsel: And it will have regard to whether it's consistently implemented, as in *Innovative* [*Sonic*]..?

Mr Rennie-Smith: ...[Y]ou can certainly draw that from those cases, yes....

Counsel: And I think you did observe that this was a beyond reasonable doubt case. And can I just ask you to read the last three lines of paragraph 13....The last three lines say..."*In the case at hand, all evidence for the possible transfer of the priority right claimed is in the hands of the appellant.*" ....So...I think you'll agree with me, the same reasoning as we saw in *Innovative [Sonic]*..?

Mr Rennie-Smith: Yes.

8. Documents Received

428. Counsel noted that BMS's solicitors in this case had indicated that they would produce certain documents to their witnesses for consideration, namely a manual of June 2002 and certain e-mails that issued between January and June 2022 [*sic* – presumably 2002]. She then asked Mr Rennie-Smith to consider carefully whether he had received those documents at any stage. Mr Rennie-Smith indicated that he had not.

D. Re-Examination

429. Counsel for BMS turned first to Case T0590/98 *Radiopharmaceuticals/AMERSHAM PLC* (ECLI:EP:BA:2003:T059098.20030430), and asked a succession of questions. Again, I do not see the relevance of this case to the case at hand. Case T0590/98 concerned the question of whether BMS Pharma could appeal a decision from an opposition commenced in the name of the DuPont Merck Pharmaceutical Company. So, just to note, it did not, *e.g.*, concern the issue of whether BMS Co had a beneficial interest in the intellectual property of BMS Pharma as a matter of Delaware law. The materials supplied to the Technical Board of Appeal in that case were clearly understood by the Board to establish that BMS Pharma Co was one and the same entity as the previously named DuPont Merck Pharmaceuticals company. I cannot discern any relevance between this case and the matter now in issue before me, namely whether BMS Co had the beneficial interest in US 165 on 17 September 2002 when it applied to file WO652.

1. Opposition at European Patent Office

430. Asked by counsel for BMS who has standing to institute an opposition at the EPO, Mr Rennie-Smith indicated that any person may do so.

431. Counsel for BMS then turned to a consideration of the rights that an opponent gets by virtue of instituting an opposition, turning in this regard to Case G0004/88. The facts underlying that case were as follows. In 1985, MAN Maschinenfabrik Augsburg-Nürnberg AG assigned to MAN Nutzfahrzeuge GmbH its operations in the commercial vehicle field together with the related industrial property rights. It subsequently merged with Gutehoffnungshütte Aktienverein AG which then changed its name to MAN AG. Following an EPO Opposition Division decision to reject an opposition entered by MAN Maschinenfabrik Augsburg-Nürnberg AG on behalf of its commercial vehicles division, MAN AG, the universal successor in title to the original opponent, lodged an

appeal, at the same time requesting that the opposition be transferred to MAN Nutzfahrzeuge as assignee of the division to which the opposition related. At the appellant's request and by a decision dated 29th April 1988, the competent Technical Board of Appeal referred the following point of law to the Enlarged Board of Appeal: is an opposition pending before the European Patent Office transferable only to the opponent's heirs or can it be transferred freely either with the opponent's enterprise or with a part of that enterprise operating in a technical field in which the invention to which the patent in suit relates can be exploited?

432. Counsel for BMS then brought Mr Rennie-Smith to the point where the Board in *MAN* observes as follows (at §2):

> "*This right available to any person, only gives rise to a subjective right for the opponent through actual institution of the proceedings. A bundle of procedural rights is then created in respect of the opponent because, in contrast to the third party who presents observations under Article 115 EPC, the opponent becomes a party to the opposition proceedings (Article 99(4) EPC). As a party he has, in particular, the right to be heard (Article 113(1) EPC), the right to request oral proceedings (Article 116 EPC) and the right to appeal against the decision of the Opposition Division (Article 107 EPC). The opponent may furthermore, if appropriate, be ordered to pay the patentee's costs (Article 104 EPC), etc.*"

433. Arising from these observations, counsel for BMS asked how the Board, in Case G0004/88 *Transfer of opposition* (ECLI:EP:BA:1989:G000488.19890424), characterises the nature of the rights that arise in an opponent by virtue of instituting an opposition. Mr Rennie-Smith responded that they are procedural rights.

434. Counsel for BMS then asked Mr Rennie-Smith to identify the circumstances in which such a bundle of procedural rights may be transferred to another person. Mr Rennie-Smith indicated that it (the bundle) "*can be transferred together with the assets of the business and the interest of which the opposition was commenced*." Asked who can appeal an opposition, Mr Rennie-Smith indicated that this could be done by any party to the opposition, the patentee, or any opponent adversely affected by the decision. Asked who in general terms would be adversely affected by a decision, Mr Rennie-Smith responded "*A party whose request is not fulfilled.*"

435. Returning to Case T0590/98, counsel reminded Mr Rennie-Smith that that case concerned whether Bristol-Myers Squibb Pharma Company could appeal an opposition that was commenced in the name of the DuPont Merck Pharmaceutical Company, Mr Rennie-Smith confirming "*We decided...it was entitled to continue it because it was the same party as had commenced, there had simply been changes of name.*" Counsel then led Mr Rennie-Smith to §2.5 of the decision in which the Board of Appeal observes as follows:

> "*The respondent's evidence could indicate any of several possible scenarios. At one extreme, the appellant might simply have licensed or authorised, exclusively or non-exclusively, another legal entity to market or sell some of its products in a certain territory, but that would not amount to a transfer of even a part of its business. Equally, at another extreme, the appellant might indeed have disposed of its entire business to a universal successor with the exception of its right to prosecute its opposition, so that apart from these proceedings it was dormant. On either scenario, and on the many possible scenarios between those two extremes, it would in the absence of evidence to the contrary remain entitled to bring and pursue this appeal.*"

436. Again, as I have repeatedly stated of Case T0590/98, I do not see the relevance of this case to the case at hand. As mentioned above, that case concerned the question of whether BMS Pharma could appeal a decision from an opposition commenced in the name of the DuPont Merck Pharmaceutical Company. So, it did not, *e.g.*, concern the issue of whether BMS Co had a beneficial interest in the intellectual property of BMS Pharma as a matter of Delaware law. The materials

supplied to the Technical Board of Appeal in that case were clearly understood by the Board to establish that BMS Pharma Co was one and the same entity as the previously named DuPont Merck Pharmaceuticals company. I cannot discern any relevance between this case and the matter now in issue before me, namely whether BMS Co had the beneficial interest in US 165 on 17 September 2002 when it applied to file WO652.

437. Counsel then asked to what extent can an opponent be divested of assets of a business and still have a right to continue with an opposition? To this, Mr Rennie-Smith responded: "[W]*hen you divest yourself entirely of everything but the opposition....And it remains in being, in the case of a company, it remains extant....It can continue.*"

2. Materials Received by Mr Rennie-Smith

438. Moving to the question of the materials that he received, counsel for BMS recalled that Mr Rennie-Smith had been asked, while under cross-examination, some questions in relation to the materials that he received for his first report, then subsequent materials that he had received, with Mr Rennie-Smith indicating, while under cross-examination, that he had received a statement of Mr. Steele, Dr Kinkeldey and Prof. Thomas in a second tranche, and perhaps also further materials. Asked whether (because a weekend had intervened in the hearings), he had a chance to refresh his memory in relation to the further materials that he received most recently, Mr Rennie-Smith indicated that he had not.

3. Assignment of 17th September 2002

439. Counsel turned next to a reference that Mr Rennie-Smith had made in his previous evidence to an assignment of 17th September 2002. Counsel brought Mr Rennie Smith to the assignment of 17th September 2002 and had him confirm that what was being assigned there was "*applications for patents and inventions in any country*", the assignors being Drs Pinto and Quan.

440. Teva has tried but (with respect) failed to make some significance of the assignment of 2002 in its written closing submissions, submitting as follows:

> "*2.8 On 17 September 2002, the Filing Date, the inventors executed an assignment of US non- provisional patent application no. 10245122 ('US122') to BMS Co (not BMS Pharma) (the '2002 Assignment'). BMS now state, US122 proceeded to grant as US patent no. 6,967,208 ('US208'), the US equivalent to the Patent. US122 was filed on 17 September 2002, the same date as the WO652 application, but was a separate and standalone US filing.*
>
> *2.9 BMS did not make discovery of 2002 Assignment but furnished a copy to Teva on 24 July 2023. Although it was addressed by Mr Rennie Smith in his Witness Statement dated 17 November 2021 (filed in Netherlands, Sweden, Italy, Czech Republic, Finland and Slovakia), inexplicably, Mr Rennie Smith was instructed to ignore the 2002 Assignment for the Irish proceedings. ('I was asked not to consider in this case.')*
>
> *2.10 On re-examination, Mr Rennie Smith confirmed that the 2002 Assignment related to US122 only, which it does. However, his attention was not drawn to the fact that US122 itself was (a) expressly related to US165 and (b) was part of the same patent family with the same docket number, PH7398....*
>
> *2.11 The significance of the 2002 Assignment for present purposes is that it demonstrates that the inventors executed and assigned a patent application to BMS Co. on the Filing Date, which (on its face) related to US165. The same step could easily have been taken in respect of US165 during the priority year but was not. Instead, a decision was made to assign US165 to BMS Pharma*."

441. Four points might be made in this regard. First, these are not discovery proceedings and I do not have the evidence before me to decide whether or not a particular document fell to be discovered. If it did (and BMS must have taken the view that it did not), it would not have made any difference. Second, it is true that BMS might have taken an alternative approach; however, the fact is that it did not and this case falls to be decided by reference to what BMS did, not by reference to what it might have done. Third, just because BMS might have taken an alternative route to the one it adopted does not point to there necessarily being any legal deficiency in the path that it chose (nor, as I conclude in this judgment, does any such deficiency appear to me to present). Fourth, one might contend that the fact that BMS took the route it did and did not choose some other route that it might have taken speaks to its satisfaction, from a legal and practical perspective, as to the route that it did take.

4. *Innovation Sonic* and *General Hospital*

442. Counsel for BMS noted that while he was under cross-examination Mr Rennie-Smith was brought to two cases Case T1201/14 *Innovation Sonic* and Case T1786/15 *General Hospital*, the details of which I have considered previously above. The following exchange then ensued between counsel for BMS and Mr Rennie-Smith:

Counsel:	*It was noted that policies featured in those cases. And you were invited to draw parallels with this case. Do you recall that?*
Mr Rennie-Smith:	*Yes....*
Counsel:	...[D]*o you recall what the policies were relied on in those cases to show? ....*
Mr Rennie-Smith:	*In the second case* [Case T/1786/15 *General Hospital*]*, the policy was a reallocation policy, as I recall....Often employees had, by their employment contract, it was said, passed rights to the patent applicant, the patent applicant company, the employer, or group of companies, could decide which company in the group would take over the right, as it were....*
Counsel:	*So, the reallocation policy was relied upon as a transfer into the person* [applicant]....
Mr Rennie-Smith:	*Yes....*
Counsel:	In the first one [Case T1201/14]*, can you remember what the policy was relied upon to show..?* [Counsel subsequently referred Mr Rennie-Smith to para.3.2.2 where, under the heading "*Implicit transfer by virtue of general policy under German law*"]....
Mr Rennie-Smith:	*The suggestion was that performing this policy, the right of priority was transferred.*
Counsel:	*....It was relied upon as a transfer. Do you recall in either of those cases any argument that under Delaware law the control of one company over the assets of another conferred an equitable interest in the patents?*
Mr Rennie-Smith:	*No, I don't recall Delaware law featuring in either case.*

14

Some Conclusions

443. What key conclusions might be reached following the consideration in previous chapters of the evidence of Dr Kinkeldey and Mr Rennie-Smith? It seems to me that the following might safely be stated.

[1] Mr Rennie-Smith confirmed that the observation of the Technical Board of Appeal at §3.1.1.3 of its decision in Case T-1201/14 *Transfer of right of priority* reflects what the Boards of Appeal draw from Article 87 in relation to succession in title, that observation being as follows:

> "[T]*he substantive requirements derivable from the EPC for a valid transfer of the right of priority may be summarised as follows: The successor in title with respect to the right to claim priority from a first application according to Article 87(1) EPC 1973 must prove that it indeed owned, (i) before the filing of the later European application, (ii) the right of priority relating to the first application for the purpose of filing the later European application claiming that priority.*" [Emphasis in original].
>
> [The following exchange took place between counsel for BMS and Mr Rennie-Smith in this regard:
>
> | | |
> |---|---|
> | Counsel: | *Can I refer you very briefly to paragraph 3.1.1.3 there in the middle of the page?* |
> | Mr Rennie-Smith: | *Yes.* |
> | Counsel: | *If you could just refresh your memory about that?* |
> | Mr Rennie-Smith: | *[Short pause]. Yes.* |
> | Counsel: | *So, that's the characterisation of at least one Board in respect of what is to be taken from Article 87 itself in terms of succession in title. Can you characterise what the Board is saying there, Mr. Rennie-Smith?* |
> | Mr Rennie-Smith: | *It's very similar to what I said just now, I think, that it must be shown that the successor in title owns a right to claim priority before the filing date of a later application, the European application. So, succession has to be the ownership by right of succession has to be proved and has been done within a year.* |

Counsel:	*Thank you. And is that a fair statement of what the Boards of Appeal draw from Article 87 generally?*
Mr Rennie-Smith:	*Yes.*]

[2] although Dr Kinkeldey initially indicated that a requirement for some kind of agreement or assignment could be drawn from Art.87 of the European Patent Convention when it comes to showing succession in title, she ultimately accepted that no such requirement falls to be drawn from Art.87. Thus, among the exchanges between counsel for BMS and Dr Kinkeldey were the following:

(i)

Counsel:	*My point, Doctor, is that ownership can change otherwise than by a contract.*
Dr Kinkeldey:	*Yeah*.
Counsel:	*Certainly under common law countries it can.*
Dr Kinkeldey:	*Of course.*
Counsel:	*So, if, in the relevant applicable law, ownership has changed other than under a contract, then ownership has changed.*
Dr Kinkeldey:	*Yeah.*
Counsel:	*You agree with that?*
Dr Kinkeldey:	*Fine, yeah.*
Counsel:	*And that would be acceptable under Article 87?*
Dr Kinkeldey:	*Yes, if the transfer of the priority right is then safe because the ownership has changed and it can be proven, fine.*

(ii)

Counsel:	...[T]*here's actually no limitation imposed by the EPC that you need an assignment, it's for national law?*
Dr Kinkeldey:	*Yeah.*
Counsel:	*And you agree with that?*
Dr Kinkeldey:	*Yeah.*

[3] the Boards of Appeal at the European Patent Office turn to national law in the absence of European Patent Convention criteria for establishing succession in title to the right of priority. This was accepted by both Dr Kinkeldey and Mr Rennie-Smith. Thus, the following exchange took place between counsel for BMS and Dr Kinkeldey:

Counsel:	*So, the general proposition here is that the question of succession in title is governed any national law?*
Dr Kinkeldey:	*Yeah.*

Counsel:	*You agree with that?*
Dr Kinkeldey:	*Yes, I do,*

and the following exchange took place between counsel for BMS and Mr Rennie-Smith:

Counsel:	...[Y]*our evidence is that in the absence of provision for how succession in title is to be determined in the EPC itself, the EPO decisionmakers essentially conduct the assessment by reference to national law?*
Mr Rennie-Smith:	Yes.

[4] the rationale for the application of national law was set out by the Technical Board of Appeal in Case T0205/14 (*Ibandronate sodium, Form QQ/TEVA*). There, it will be recalled, the appellants contested the entitlement of the patent in suit to the priorities from US applications Nos 60/604, 026 of 23rd August 2004 (P1) and 60/690,867 of 16th June 2005 (P2). They argued that the respondent had failed to prove to the required standard that, on the date of filing of the international application number PCT/US2005/030500, published as WO 2006/024024, the rights of priority derived from the US provisional applications (P1) and (P2), both filed in the name of the three inventors, had been validly transferred to the respondent. As a consequence, the date of filing of the international application WO 2006/024024 was the effective date for determination of the relevant state of the art. The Technical Board of Appeal dismissed the notion of approaching the question of succession in title as a matter governed by the EPC because (see §3.6.2):

> "[T]*his would exclude the possibility of a transfer by operation of law which can only be established by reference to a (comprehensive) legal system. Also the board's assessment of the evidence adduced will inevitably need to be made by reference to defined formal and material requirements.*"
>
> (The interest value of this case is perhaps heightened by the fact that it was a case where Teva asked the European Patent Office to recognise a right of priority on the basis of equitable title and succeeded, under Israeli law, on something that was less than legal title. But the compelling part of the decision, for present purposes, is the rationale that the Technical Board of Appeal gives for going back to the applicable national law to decide who owns what. And the Board says, in effect, that if it was to try and 'cobble together' something under EPC rules, that would exclude the possibility of a transfer by operation of law which can only be established by reference to a (comprehensive) legal system, not an 'immature' legal system such as the European Patent Convention which does not seek to be all-embracing.)

[5] it follows that the assessment of whether or not a successor in title owns the right at the relevant time is to be undertaken under national law – the entire system of national law and not just portions of it.

[6] if the right to the priority document or to claim priority is recognised under

applicable national law at the relevant time, *i.e.* the time of the application invoking priority, no supervening requirement will be imposed under the European Patent Convention by the EPO Boards of Appeal, *e.g.*, by requiring an assignment, or by rejecting equitable ownership that is accepted under the applicable national law. Thus, the following exchange transpired between counsel for BMS and Mr Rennie-Smith:

Counsel:	...[I]*f ownership of the priority right is established under national law, does the EPC or do the EPO decision makers apply any additional requirement over national law to the question of succession in title?*
Mr Rennie-Smith:	*No, the basic principle is you decide what national law applies and then -- which is a matter of evidence, obviously you can't know all the national laws, and then having established what national law, you see whether you're satisfied that, according to the criteria of that law, there has been a transfer.*
Counsel:	*Thank you. So, just two follow on questions just to make sure I'm very clear of what you're saying. Is an assignment ever required if the applicable national law does not require it...Mr. Rennie-Smith?*
Mr Rennie-Smith:	*....No, there's no requirement, as such, for an assignment. If, hypothetically a national law said the only possible way would be by some particular formality, then that would have to be demonstrated.*
Counsel:	*Thank you. And is equitable ownership of the right to priority ever rejected by the EPO decision makers if it would be sufficient under the applicant national law?*
Mr Rennie-Smith:	*There have been examples of where it's been argued and it's been rejected. There's no reason why, if it was allowable under a national legal system and demonstrated to have taken effect under those criteria of that system then that would be acceptable.*

Dr Kinkeldey appears to have agreed with this analysis. Thus, she confirmed that (i) an agreement or assignment was not required to show succession in title if the applicable national law did not require it, and (ii) that equitable ownership would not be rejected if it was sufficient under national law. As to (i) the following exchange occurred between counsel for BMS and Dr Kinkeldey:

Counsel:	*My point, Doctor, is that ownership can change otherwise than by a contract.*
Dr Kinkeldey:	*Yeah.*
Counsel:	*Certainly under common law countries it can.*
Dr Kinkeldey:	*Of course.*
Counsel:	*So, if, in the relevant applicable law, ownership has changed other than under a contract, then ownership has changed.*
Dr Kinkeldey:	*Yeah.*
Counsel:	*You agree with that?*
Dr Kinkeldey:	*Fine, yeah.*
Counsel:	*And that would be acceptable under Article 87?*
Dr Kinkeldey:	*Yes, if the transfer of the priority right is then safe because the ownership has changed and it can be proven, fine.*

As to (ii) the following exchange occurred between counsel for BMS and Dr Kinkeldey:

Counsel:	...[I]*n your second report you're a bit more definitive and you say that equitable title is not sufficient to qualify as successor in title. That's quite a strong statement.*
Dr Kinkeldey:	*Yeah, I agree.*
Counsel:	*Do you stick by that statement, Doctor?*
Dr Kinkeldey:	*I would moderate it in the way that if national law allows it, and that is the decision J 19/86* [in fact, Case J-19/87 *Assignee*],***** *then equitable title is apparently all right.*

***** There, as mentioned above, the applicant for a European patent had previously been advised that the assignment to him of the invention and the United Kingdom priority patent application had no legal effect because he had not signed it. However, according to the reasoned expert opinion of an English patent barrister, which the Board accepted as correctly representing relevant English law, the assignment did have the legal effect that the applicant became the owner of the invention and entitled in equity (*i.e.,* he had an equitable title) to the United Kingdom application. He was

> entitled to apply for and be granted a European patent in respect of the invention the subject of the United Kingdom application and also, for the purpose of filing the European patent application, a right of priority.

[7] as regards equitable ownership, Dr Kinkeldey (i) shifted from the position expressed in her report, (that the acceptance in Case J 19/87 *Assignee* of equitable ownership of the priority document under English law should be confined to its own facts), to (ii) accepting that Case T-0577/11 *Entitlement to priority*,[4] confirmed that the ability to specifically enforce the right to full ownership is key to acceptance of equitable ownership as a basis to claim priority. Of note in this regard is the following exchange between counsel for BMS and Dr Kinkeldey:

> Counsel: *So the way I read what the Board is saying there and the way Mr. Rennie-Smith reads it is that the distinction between the two situations that the Board is drawing is that in the English case the applicant had the right to call for the assignment of the full title. So, essentially, the equitable ownership was, in substance, the full ownership because the applicant, at the relevant time, could call for the perfection of the title*.
>
> Dr Kinkeldey: *Yeah.*
>
> Counsel: *Whereas in this case, the applicant could not call for the perfection of the title at the relevant time. And you'll see that in the last four lines: "...in relation to the transfer of economic ownership only. It was not intended that the legal title too..."*
>
> Dr Kinkeldey: *Just a second, sorry, I'm lost. The last lines of what, which paragraph?*
>
> Counsel: *Apologies, this is on page 75* [of the judgment]*, the last four lines of the first paragraph on that page.*
>
> Dr Kinkeldey: *First paragraph. Okay, thank you. Yeah.*
>
> Counsel: *So the first paragraph: "...in relation to the transfer of economic ownership only. It was not intended that the legal title too should be transferred as from the earlier date,*

[4] *I.e.* Case T-0577/11 (*Entitlement to priority*) (ECLI:EP:BA:2016:T057711.20160414). There, it will be recalled, an argument was made that there was an economic right under Dutch law, and ultimately the Board of Appeal rejected it. What is significant about the case is that in it the Technical Board of Appeal essentially crystallised what it is about beneficial ownership that makes it a satisfactory basis upon which to assert priority. The essence of the decision was the distinction that the Board drew between the equitable ownership that presented in J-19/87 and the economic interest asserted under Dutch law whereby there was no power in the owner of the economic interest to require the legal interest to be assigned to it.

	nor could it have been acquired." That's the important thing. It couldn't have been acquired. The person who had the economic ownership, this concept under Dutch law, that concept was not a right whereby they could require the assignment to them of the full right, isn't that right?
Dr Kinkeldey:	*According to the view of the Board, yes.*
Counsel:	*According to the view – and that is the distinction that the Board is drawing between –*
Dr Kinkeldey:	*To the English case.*
Counsel:	*– this case and the J 19/87 case.*
Dr Kinkeldey:	*Mm-hmm.*

As Dr Kinkeldey clearly agrees in the above-quoted text with the analysis proffered by counsel as to why the Board was making the distinction it did, I must admit to surprise at finding the proposition canvassed in Teva's submissions that Case T-0577/11 falls to be read as constraining the recognition of equitable title as sufficient title. In truth, what the case does is to succinctly identify what it is about equitable title that renders it a satisfactory basis on which to claim priority.

In passing, I note that the text at p.75 of the judgment in T-0577/11 to which counsel for BMS refers in the above-quoted text seems to me to be of significance in this case, in circumstances where, as will be seen later in the main text , Mr Steele, the expert on Delaware law called by Teva, spoke of the right recognised in the US District Court case of *Hologic Inc* v. *Minerva Surgical Inc* 163 F supp. 3d 118 as providing a sufficient equitable interest to provide standing to sue as an 'economic right'. Of note in this regard is the following exchange between counsel and Mr Steele when the latter was cross-examined:

Counsel:	...[C]*an I ask you to confirm, did you say on a number of separate occasions to the Court in Finland that BMS Co enjoyed beneficial interest in the patent that we're all discussing in this case?*
Mr Steele:	*I did.*
Counsel:	*And I take it, Mr. Steele, that when you acknowledge that it had a beneficial interest, you were acknowledging that as an ownership interest in the patent, though you did distinguish it from legal interest, isn't that right?*
Mr Steele:	*In part. But actually, as...Judge Robinson's case provides* [*i.e.* Hologic Inc. *v.* Minerva Surgical, Inc. *163 F. Supp. 3d 118 (D. Del. 2016)*], *it's an interest economically that allows, under the context of this case,*

	the parent who doesn't have legal title to the patent to protect its economic rights through equity.
Counsel:	*No, but –*
Mr Steele:	*So, it's equitable standing.*
Counsel:	*But sorry, Mr. Steele, just to be clear, when you talk about economic rights, you're talking about rights you have as a consequence of beneficial ownership, isn't that correct?*
Mr Steele:	*I think that's correct, yes.*

In a still later exchange between counsel for BMS and Mr Steele while under cross-examination, the following transpired:

Mr Steele:	...[W]*hen she* [Robinson J. in *Hologic*] *states what her holding is, she states that she finds equitable standing which gives the opportunity for equitable remedy and to seek equitable relief generally, no more than that.*
Counsel:	*Because she found – she couldn't have made that finding unless she had already found that the beneficial owner of the patents in question was the parent. Isn't that correct?*
Mr Steele:	*It's correct that she found there was a beneficial ownership that gave rise to the standing, yes.*

What I would just note at this juncture is that an 'economic right' that confers a right to call for specific performance of an obligation to assign legal title, is, by definition, beneficial ownership and is the kind of equitable interest recognised under the European Patent Convention as a sufficient basis to claim priority. I do not understand it to be disputed in this case that BMS Co could have called directly on BMS Pharma Co. to assign full legal title in US 165 to it at any point.

[8] it follows that Article 87 of the European Patent Convention imposes (i) no requirement for an agreement or an assignment before a company can be regarded as successor in title to the priority right, and (ii) no constraint or block on equitable ownership of a priority document as a proper basis upon which to claim priority.

[9] it necessarily follows from [7] that no such requirements can therefore impact on the construction or implementation of s.25 of the Patents Act 1992, as amended.

VI. THE EVIDENCE AS TO UNITED STATES FEDERAL LAW

15

Some Prefatory Observations

444. Before proceeding to consider the evidence before me as to United States federal law and the laws of the State of Delaware, it is useful briefly to pause and consider how the law operates as regards the receipt of evidence of foreign law in an Irish court. I have been referred to case law and commentary, which I consider below.

i. *Sussex Peerage Case* (1844)
11 Cl & F 85 (HL)

445. This was an unsuccessful claim to a royal peerage by a grandson of King George III. In the case the key question was whether the claimant's deceased father – Prince Augustus Frederick, the Duke of Sussex – had been married or not. In the course of the House of Lords' deliberations, Lord Brougham observed (at 115) that "[I]*t is perfectly clear that the proper mode of proving a foreign law is not by showing to the House the book of the law; for the House has not organs to know and to deal with the text of that law, and therefore requires the assistance of a lawyer who knows how to interpret it.*" Lord Denman in the same case observed, at 115, that "*A skilful and scientific man must state what the law is, but may refer to books and statutes to assist him in doing so*".

ii. *Earl Nelson* v. *Lord Bridport*
(1845) 8 Beav. 527 (Rolls Court)

446. This was a case arising from the fact that Admiral Lord Nelson had been granted an estate in Italy by a grateful King of the Two Sicilies. Nelson left the estate to the future Earl Nelson (his older brother) subject to certain trusts. This case decided that as the admiral could not subject the future earl to a course of succession different from that which accorded with the grant and the law of Sicily, so neither could he subject the earl, as such, to any duties or obligations different from the duties and obligations which by the grant and the law of Sicily were annexed to the admiral's own holding. In the course of his judgment in the case, Lord Langdale, MR, adjudged as follows when it came to the mode in which a foreign law ought to be proved in an English court of justice (at 534–536):

> "*With foreign laws an English Judge cannot be familiar; there are many of which he must be totally ignorant: there is, in every case of foreign law, an absence of all the accumulated knowledge and ready associations which assist him in the consideration of that which is the English law, and of the manner in which it ought to be applied, in a given state of circumstances to which it is applicable. He is not only without the usual and necessary assistance afforded by the accumulated knowledge and able suggestions contained in the arguments which are addressed to him, but he is constantly liable to be misled by the erroneous suggestion of analogies which arise in his own mind, and are pressed upon him on all sides. These difficulties are obvious enough, even in cases in which he may have before him the very words of that which is proved to have been the law applicable to the events in question. Even if we suppose it to be proved, that the law has not been legislatively repealed or varied, and has not fallen into disuse, and that the words have been accurately translated, still the words require due construction, and the construction depends on the meaning of words to be considered with reference to other words not contained in the mere text of the law, and also with reference to the subject-matter, which is not insulated from all others. The construction may have been, probably has been, the subject of judicial decision: instead of one decision, there may have been a long succession of decisions, varying, more or less, from each other, and ultimately ending in that which alone ought to be applied in the particular case.*

The difficulty which arises under such circumstances is obviously very great; but it is vastly increased, when the law itself, or the form or collocation of words in which the law is expressed, has never been authoritatively expounded, but is to be discovered from decisions or usages, or from the opinions of unauthorised writers, who may have written much that is acknowledged to be existing law, and also, in the same books, much which is contrary to existing law. The decisions were subject to be, and may have been, altered by subsequent decision, and the precise application of them to the case in question, may only be ascertainable, by means of accurate historical and legal deduction from all that has passed in the Courts on the subject; and a Judge who seeks information as to a foreign law, has not, in himself, the means of distinguishing the correct from the incorrect proposition of a text writer. Whoever has considered the nature of the difficulties which frequently arise in our own Courts, in the investigation of English law applicable to particular cases, and the mode of reasoning and investigation by which it is endeavoured to surmount those difficulties, will perceive what presumption it would often, nay generally, be, in an English Judge to attempt to apply the same process to the investigation of a foreign law, and the consideration of its proper application to particular cases. The rule of English law, that no knowledge of foreign law is to be imputed to an English Judge sitting in a Court of only English jurisdiction, is undoubtedly well founded.

And as cases arise, in which the rights of parties litigating in English Courts cannot be determined, without ascertaining, to some extent, what is the foreign law applicable in such cases, the foreign law and its application, like any other results of knowledge and experience in matters of which no knowledge is imputed to the Judge, must be proved, as facts are proved, by appropriate evidence, i.e., by properly qualified witnesses, or by witnesses who can state, from their own knowledge and experience, gained by study and practice, not only what are the words in which the law is expressed, but, also, what is the proper interpretation of those words, and the legal meaning and effect of them as applied to the case in question."

iii. *O'Callaghan* v. *O'Sullivan*
[1925] IR 90 (SC)

447. Here, the appellant Catholic parish priest, was removed from his parish by a decree of removal issued by the bishop of the diocese in which the parish was situated. The bishop did not mince his words. The decree of removal commences:

"*Your people's hatred of you, and your ill administration of the temporal goods of your parish, even if they had not already been matters of notoriety throughout our Diocese, have been proved conclusively by admissions made by you...*"

448. It was admitted that the legal relationship of the parties was contractual and governed by the laws, ordinances, and canon laws of the Roman Catholic Church. The appellant sought a declaration that the decree was illegal and void, amongst other matters, on the grounds that canon law had not duly been observed. It was contended for the appellant that canon law was not foreign law requiring proof by experts; that the *Codex Juris Canonici* contained the contract between the parties, constituting a written contract in a foreign language to be construed by the court accordingly. At the trial a TCD classics scholar gave evidence for the appellant as to the translation of portions of the *Codex* but he had no special knowledge of canon law. For the respondent two professors of canon law gave evidence that there had been no breach in the observances of canon law.

449. The Supreme Court held that Catholic canon law is foreign law which must be proved as a fact and by the testimony of expert witnesses according to the well-settled rules as to proof of foreign law. In the course of his judgment for the court, Kennedy C.J. observed as follows, at 119-120:

"[T]*he Canon Law applicable to the case must be proved as a matter of fact by expert witnesses as foreign law in these Courts. That has been done by two witnesses called on behalf of the defendant. The testimony of both is to the same effect. No other skilled evidence has been given. In my opinion, the Court must accept that evidence, unless obviously false or discredited in some way....*

The rule is that the foreign law applicable to a case must be taken from the statement of the expert witness as to what the law is, and not from textbooks or codes referred to by him. During the hearing of the Sussex Peerage Case*...Dr Wiseman was observed to refer to a book, presumably some volume of Canon Law, and a discussion arose, whereupon the rule was restated; Lord Brougham put it thus in a passage very often quoted: 'The witness may refer to the sources of his knowledge,* but *it is perfectly clear that the proper mode of proving a foreign law is not by showing to the House the book of the law; for the House has not organs to know and to deal with the text of that law, and therefore requires the assistance of a lawyer who knows how to interpret it.' Lord Denman said: 'A skilful and scientific man must state what the law is, but may refer to books and statutes to assist him in doing so,' and he referred to the rule as laid down in* Baron de Bode's Case*....There the question arose as to whether a French advocate could be permitted to prove the effect of a certain decree without proving the original text of the decree, and it was held that not merely was the evidence admissible but it was the proper evidence of the state of law created by the decree. An objection was taken, based on the rule as to secondary evidence of written instruments. 'But,' said Lord Denman... 'there is another general rule: that the opinions of persons of science must be received as to the facts of their science. That rule applies to the evidence of legal men; and I think it is not confined to unwritten law, but extends also to the written laws which such men are bound to know. Properly speaking, the nature of such evidence is, not to set forth the contents of the written law, but its effect and the state of law resulting from it. The mere contents indeed might often mislead persons not familiar with the particular system of law: the witness is called upon to state what law does result from the instrument.'" *****

* With every respect to a rightly respected judge, Kennedy C.J. appears to suggest in the above-quoted text that Lord Denman made the reference to there being another general rule, *etc.* in the *Sussex Peerage Case* (in July 1844). However, Lord Denman made these observations six months later in *Baron de Bode's Case* (1845) 8 QB, 208, 115 E.R. 854 (KB). There, a party claiming to have been the owner of lands, by virtue of a cession to him from A., since deceased, offered evidence, before any other proof of the cession, that A. actually managed the property, and, while so managing, declared that he did so in the name of the now claimant. It was in giving judgment in that case that Lord Denman (in the Court of King's Bench) observed as follows (at 250-251):

> "*The witness, upon being questioned as to the state of law in France in 1789, refers to a decree of that date. The form of the question is, I think, immaterial: in effect, the witness is asked to speak to the decree. It is objected that this is a violation of the general principle, that the contents of a written instrument can be shewn only by producing the instrument or accounting for the non-production. But there is another general rule: that the opinions of persons of science must be received as to the facts of their science. That rule applies to the evidence of legal men : and I think it is not confined to unwritten law, but extends also to the written laws which such men are bound to know. Properly speaking, the nature of such evidence is, not to set forth the contents of the written law, but its effect and the state of law resulting from it. The mere contents, indeed, might often mislead persons not familiar with the particular system of law : the witness is called upon to state what law does result from the instrument.*"

iv. *MacNamara* v. *Owners of the SS "Hatteras" (No. 2)*
[1933] IR 675 (SC)

450. Here, the defendant shipowners by two bills of lading (which were similar) agreed to carry certain hogsheads of leaf tobacco from Norfolk, USA, to Dublin, and there to deliver same to the plaintiffs in good order and condition. A dispute arose between the parties following the delivery of the hogsheads in Dublin. Both parties concurred in stating two questions of law in the form of a special case for the opinion of the court. That special case had gone before Meredith J. in the High Court who had decided the two questions posed as though he was presented with an English law contract. On appeal the Supreme Court had held that the bills of lading were American contracts, and as such should be construed by American law, and that that law had to be proved or admitted before the court would be competent to decide the questions of law submitted in the special case. The Supreme Court therefore, discharged the order of Meredith J. and remitted the special case to him to be determined freshly. Meredith J. proceeded accordingly and again decided the two questions posed. In his judgment, following an appeal from the second hearing of the Special Case, FitzGibbon J. observed, amongst other matters, as follows, at 699-700:

> "[I]*f an expert in the law of a foreign country, whose qualifications and credibility are unimpeached, gives evidence upon oath that the law of that country is so, or that a particular contract, or clause in a contract, is, or is not, valid according to the law as administered in the Courts of that country, and his testimony is not contradicted by the evidence of another expert, or broken down by cross-examination, the Court which has to decide the question is just as much bound to accept and act upon that evidence as it would be to accept and act upon the evidence of any credible and uncontradicted witness upon any other question of fact or opinion. In the words of Lord Stowell,* oportet discentem credere [*i.e.* 'the learner must believe']. [14] *The Court cannot reject the evidence of the expert because it would itself have come to a different conclusion on perusal of the text of the foreign law or on consideration of the terms of the document which is to be interpreted or whose validity is to be decided in accordance with that law....*
>
> [I]*f the evidence of the experts is conflicting, either as to the text of the law, or as to its interpretation, or as to the way in which the question at issue would be decided by the foreign court which might have to administer the law, then the Court must make up its own mind as best it can, using the material at its disposal, and deciding between the experts as it would have to do if they were giving their opinion upon any scientific question....*"

v. *McC* v. *McC*
[1994] 1 IR 293 (HC)

451. In this case, the plaintiff and defendant were married in England and then moved to Hong Kong. They were divorced there, and a Hong Kong court made, amongst other matters, on consent, a maintenance decree in favour of the plaintiff. The defendant left Hong Kong and came to live in Ireland. The plaintiff took up residence in England. The defendant defaulted on payments of maintenance and the plaintiff instituted proceedings for the arrears in the Circuit Court. The enforceability of the Hong Kong order in this country was raised as a defence, and was tried as a preliminary issue. In the course of his judgment in the case, Costello J., as he then was, relied (at 296) on the *Hatteras* case as authority for the proposition that "*When a dispute arises between experts (as has occurred in this case) as to how a foreign statute or ordinance should be construed then the court in this country may resolve the dispute by itself, construing the instrument*". This is an observation that would have had more significance in this case were it not for the fact that significantly, each side's expert witness on Delaware law, both of whom are former senior members of that state's judiciary, gave evidence which was to the effect that BMS Co was the equitable owner of US165.

vi. *Walsh* v. *National Irish Bank Ltd*
[2013] IESC 2

452. Here, the Supreme Court was concerned with a possible obligation on the part of National Irish Bank to make disclosure of what would ordinarily be considered confidential information concerning customer accounts held at its branch in the Isle of Man. The disclosure was sought by Mr Walsh in his capacity as an authorised officer of the Revenue Commissioners. So the case raised issues of Isle of Man law. It was in this context that Clarke J., as he then was, in his judgment for the Supreme Court observed as follows, at §§6.2-6.3:

> "[1] [I]*n the ordinary way, foreign law is treated as a matter of fact to be established, in the Irish courts, in the ordinary way by sworn evidence of that fact.*
>
> [2] *An affidavit from an appropriately qualified lawyer is the normal way in which evidence as to foreign law is to be established....*
>
> [3] [A] *party who wishes to dispute such evidence is required to put forward its own contrary evidence from a likewise suitably qualified lawyer.*
>
> [4] *In the case of a dispute, then it may well be necessary that both lawyers be cross-examined so as to assist the Irish court in coming to a conclusion....*
>
> [5] [R]*eference to case law or other materials from foreign jurisdictions is not an appropriate way, in the absence of evidence from a suitably qualified lawyer making reference to such materials, to establish the law concerned.*
>
> [6] *Irish courts may...have occasion to consider the case law of other jurisdictions which may provide persuasive authority as to the proper approach to be adopted in like circumstances in Ireland. However, when so doing the Irish courts are simply referring to materials which may be of assistance in interpreting Irish law.*
>
> [7] *Where an Irish court is required, for the purposes of determining the proper result of litigation, to reach a conclusion as to relevant foreign law, then such a conclusion cannot be reached simply on the basis of counsel referring the Irish court to statute or case law from the relevant jurisdiction.*"

vii. *McCaughey* v. *IBRC*
[2013] IESC 17

453. In 2006, the plaintiff was solicited by the first defendant bank to invest US$1m in a property fund, with US$620,000 of that sum having been borrowed from the bank. The second defendant was incorporated by the bank as a vehicle for participation in the fund. In 2009, the plaintiff issued proceedings against the defendants, claiming rescission of the 'Commitment Agreement' (which 'committed' him to pay US$1m for the investment), the loan agreement, the return of his investment and damages. For present purposes, what is of note is the observation of Hardiman J., at p.45, affirming the longstanding position that "*The content of foreign law requires to be proved as a fact in this jurisdiction and in most Common Law jurisdictions*."

viii. *Lehane* v. *Dunne*
[2018] IECA 7

454. This was a post-'Celtic Tiger' crash case in which complicated issues presented before the court as to (i) what was the effect of United States bankruptcy law so far as certain Irish proceedings was concerned and whether the determination of certain Irish proceedings created a *res judicata* or collateral estoppel such as would bind a United States trustee in bankruptcy from relitigating matters in the United States courts. For present purposes, of note are the following observations of Hogan J., at §§17-18:

"*17.* *The first thing to note is that an issue of foreign law is always a question of* fact *for an Irish court. The foreign law is, of course, proved by evidence normally given in the first instance in affidavit form by a suitably qualified lawyer from the jurisdiction in question. Where there is a dispute as to what the law is or where the foreign law is doubtful or even obscure on the point in question, the Irish court must ultimately adjudicate on that question and form a view as to what the foreign law provides, any uncertainties on this question notwithstanding. But it is clear that it does so* qua *finder of fact.*

18. *This is clear from a trilogy of Supreme Court decisions:* O'Callaghan *v.* O'Sullivan *[1925] 1 I.R. 90;* MacNamara *v.* Owners of the Steamship 'Hatteras' *[1933] I.R. 675 and* Kutchera *v.* Buckingham International Holdings Ltd. *[1988] I.R. 61. As Walsh J. said in* Kutchera *([1988] I.R. 61, 68):*

> *'These cases quite clearly establish that in Irish law foreign law must generally be proved by expert evidence…These cases also establish that if there is any conflicting evidence as to what is the foreign law, or what is the correct interpretation of the foreign law, then it is a matter for the Irish court to decide as between the conflicting expert testimonies.'"*

[Curiously, despite the importance that Hogan J. attaches to *Kutchera*, I was not referred to it by either side in these proceedings, though reference is made to it in *McGrath on Evidence* to which I was kindly referred. In *Kutchera*, the plaintiff, who resided in South Africa, entered into an agreement through Bahamian agents to lend a sum of Canadian dollars to the defendant, a public company incorporated under the laws of Alberta, Canada. The agreement was executed in Canada. The repayment of the sum borrowed was to be made to the plaintiff's London bankers. Further provisions of the loan agreement entitled the plaintiff, in the event of default, to demand of the defendant company that it allot to him a number of shares in the company and to nominate a number of persons to be appointed to its board of directors. A clause of the loan agreement provided that it was to be construed and governed by the laws of the Republic of Ireland, to be deemed to have been made in the Republic of Ireland and to be subject only to the jurisdiction of the Irish Courts. The Supreme Court reversed a refusal of jurisdiction by the High Court. It was in this context that Walsh J. (with whom Hederman J. agreed) made the above observations.]

ix. *Data Protection Commissioner* v. *Facebook Ireland Ltd*
[2019] IESC 46

455. Following a complaint by the second defendant regarding the transfer of his personal data to the United States by the first defendant, the plaintiff formed the view that she had concerns relating to the validity of Commission Decision 2010/87/EU of 5 February 2010 on standard contractual clauses for the transfer of personal data to processors established in third countries under Directive

95/46/EC of the European Parliament and of the Council (the SCC decision). The plaintiff initiated proceedings in the High Court seeking that the court make a reference pursuant to Article 267 TFEU to the CJEU concerning the validity of the SCC decision. The first defendant sought leave to appeal directly to the Supreme Court against the decision to make an Article 267 TFEU reference and also sought to appeal against certain findings as to United States law made by the High Court. In the course of his judgment, Clarke C.J. observed as follows, at §§4.1-4.4, essentially reiterating some of the key principles that have already been identified above:

> "4.*1* *It is a well-established principle of Irish law that findings made by a court in relation to foreign law are treated as findings of fact.*
>
> *4.2* *In* O'Callaghan *v.* O'Sullivan *[1925] 1 I.R. 90, Kennedy C.J. stated at p. 112 that foreign law:-*
>
> > *'... applicable to the circumstances of a particular case must be proved as a fact in the particular case, and…it must be so proved by the testimony and opinion of competent expert witnesses shown to possess the skill and knowledge, scientific or empirical, required for stating, expounding, and interpreting that law.'*
>
> 4.3 *Similarly, in* MacNamara *v.* Owners of the Steamship 'Hatteras' *[1933] I.R. 675, FitzGibbon J. stated at page 698:-*
>
> > *'Before I deal with the appeal itself I think it is well that I should state my view upon the real issue of fact which the learned Judge had to decide. Foreign Law, i.e., the law of a foreign country, must be proved as a matter of fact in our Courts, if a question depending upon that law is in dispute.'*
>
> 4.4 *This principle was reiterated more recently by Hardiman J. in* McCaughey *v.* Irish Bank Resolution Corporation *[2013] IESC 17, where he stated at para. 96:-*
>
> > *'The above findings have been made by the learned trial judge in the course of a meticulous judgment and after a hearing in which both the plaintiff and witnesses on his behalf, including expert witnesses on New York Law, gave evidence and were cross-examined. Similarly, most of those involved on the side of the Bank and their advisers, including each sides expert on New York Zoning Law gave evidence and were cross-examined. The content of foreign law requires to be proved as a fact in this jurisdiction and in most Common Law jurisdictions. I am therefore of the view that the findings set out above, both as to the significance of the zoning issue and as to the state of mind of Mr. McCaughey, are findings of fact made by the judge of the High Court after hearing appropriate evidence to allow him to make them.*'"

x. *McGrath on Evidence*, 3rd ed., 2020,
§§6-152-160

456. In this textbook the learned authors state as follows, under the heading "*Proof of Foreign Law*":

> "*6-152* *It is well established that expert evidence is not admissible in respect of*

any matter of domestic law.[432] *However, it is not only admissible but is mandatory in respect of matters of foreign law, which is required to be proved as a fact,*[433] *and the evidence of a non-expert as to a foreign law is inadmissible.*[434]

6-153 *In general, the dividing line between domestic law and foreign law*[435] *is straightforward but it should be noted that, where the construction or application of legislation that is common to both Ireland and England arises in the context of a question of English law, this will be considered to be an issue of foreign law.*[436] *Similarly, where the interpretation and application in another jurisdiction of a convention that has been incorporated into domestic law (such as the European Convention on Human Rights) arises, this again is considered to be a question of foreign law.*[437]

6-154 *In order for evidence of foreign law to be admissible, however, an issue of the foreign law in question must arise for determination in the proceedings.* [438] *While the decisions of the courts of other States may be cited before the Irish courts as persuasive authority, expert evidence of foreign law is not admissible for this purpose. In* O'Brien *v* Clerk of Dáil Eireann*,*[439] *it was held that an expert report from a professor of constitutional law at Harvard Law School, in which he gave evidence on US constitutional law,*[440] *was not admissible in proceedings which concerned a dispute as to the plaintiff's rights under the Irish Constitution and the European Convention on Human Rights. Kelly P observed that, while it was open to the plaintiff to cite foreign law as persuasive authority in the course of his legal submissions, this did not provide any justification for admitting expert evidence of foreign law.* [441]

6-155 *The leading Irish case on the proof of foreign law is* O'Callaghan *v* O'Sullivan*,* [442] *where it was held that, where an issue of foreign law arises, it:*

A.

> *'…must be proved as a fact in the particular case, and… it must be so proved by the testimony and opinion of competent expert witnesses shown to possess the skill and knowledge, scientific or empirical, required for stating, expounding, and interpreting that law."*[443]

6-156 *Thus, foreign law can only be proven by the evidence of a suitably qualified lawyer and, in the absence of such evidence, cannot be established by referring to statutory provisions or case law from the relevant jurisdiction.*[444]

6-157 *It is ultimately a question of fact as to whether a person has sufficient expertise in a foreign law but it is likely that a person will have the requisite expertise if he or she is a practitioner,*[445] *a former practitioner,* [446] *or a person qualified to practise*[447] *in the particular foreign jurisdiction, or is person who, though unqualified, has acquired sufficient expertise by academic study*[448] *or, in matters of commerce, by practical experience.*[449] *However, regardless of how the witness has acquired his or her expertise, he or she should be an independent expert.*[450]

6-158 *Where an expert witness gives evidence upon a matter of foreign law, the general rule is that it is the testimony of the witness which constitutes evidence on that issue and not the textbooks or other legal materials referred to by him.*[451] *This is because the court 'has not organs to know and to deal with the text of that law, and therefore requires the assistance of a lawyer who knows how to interpret it."*[452] *Thus, a judge is generally not permitted to consult the sources used by the expert,*[453] *but he may do*

so when the evidence given is unclear[454] *or where there is a conflict between the experts.*[455] *In no circumstances, however, may the judge go beyond the sources used by the expert and conduct his or her own research into foreign law.*[456] *Furthermore, where admissible expert evidence of foreign law is tendered, the court is required to accept it 'unless obviously false or discredited in some way'*[457] *and the court cannot reject the evidence of the expert because it would itself have come to a different conclusion on perusal of the text of the foreign law or on consideration of the terms of the document that falls to be interpreted or whose validity is to be decided in accordance with that law.*[458] *However, where the expert evidence establishes that a discretion is enjoyed by a court under the foreign law, an Irish judge will not necessarily be bound by the view of an expert as to how that discretion should be exercised.*[459]

6-159 *If there is a conflict between the experts as to either the content of the foreign law, its interpretation, or how the question at issue would be decided by a court in a foreign jurisdiction, then, in accordance with the approach laid down by Fitzgibbon J in* MacNamara *v* Owners of the SS 'Hatteras'*,*[460] *'the court must make up its own mind as best it can, using the material at its disposal, and deciding between the experts as it would have to do if they were giving their opinion upon any scientific question'.*[461] *In* Unicredit Global Leasing Export GmbH *v* Business Aviation Limited*,*[462] *McDonald J observed that, ordinarily, 'a court would find it difficult to resolve a dispute between experts as to foreign law without cross-examination of the experts'.*

6-160 *As noted above, an issue of foreign law is regarded as a matter of fact.*[463] *Therefore, the finding of the court on the issue has no precedential value and if the point arises again, it must be decided anew by reference to fresh expert evidence.*[464] *It also follows that the determination of the trial judge on the issue of foreign law is regarded as a finding of primary fact for the purposes of any appeal from that determination.*[465]

[432]. *O'Brien v Clerk of Dáil Eireann [2016] IEHC 597 at [24]–[25], [2016] 3 IR 384 at 397. See also SPUC v Grogan (No. 3) [1992] 2 IR 471 at 475; F v Ireland [1995] 1 IR 345; Glancré Teoranta v Cafferkey [2004] IEHC 123 at [10]-[11], [2004] 3 IR 401 at 407; O'Carroll v Diamond [2005] IESC 21 at [31], [2005] 4 IR 41 at 56. Cf. Byrne v Conroy [1998] 3 IR 1 at 10 (affidavits of lawyers and economists, whilst of some help in relation to the question of whether a particular offence was a revenue offence within the meaning of s.50 of the Extradition Act 1965, were not determinative of the question because it was a matter of Irish law).*

[433]. *Data Protection Commissioner v Facebook [2019] IESC 46 at [4.1]; Unicredit Global Leasing Export GmbH v Business Aviation Limited [2019] IEHC 139 at [74]; Official Assignee in Bankruptcy in the Estate of Sean Dunne v Dunne [2018] IECA 7 at [17]; Friends of the Irish Environment v The Government of Ireland [2018] IEHC 740 at [23]; Brien v Clerk of Dáil Eireann [2016] IEHC 597 at [26], [2016] 3 IR 384 at 397; McCaughey v Irish Bank Resolution Corporation [2013] IESC 17 at [96]; O'Callaghan v O'Sullivan [1925] 1 IR 90 at 112; MacNamara v Owners of the Steamship "Hatteras" [1933] IR 675 at 698–700; Kutchera v Buckingham International Holdings Ltd [1988] IR 61 at 68; McMahon v McDonald, unreported, High Court, 3 May 1988 at 29; Attorney General v Pocevicius [2013] IEHC 229 at 21. See also Wright-Morris v Irish Bank Resolution Corporation Ltd (in special liquidation) [2013] IEHC 385 at [25], [2014] 3 IR 468 at 480, where it was held that the burden of proving foreign law is on the party asserting a claim or defence based on foreign law.*

[434]. *Attorney General v O'Gara [2012] IEHC 179 at [7.2]. See also Friends of the Irish Environment v The Government of Ireland [2018] IEHC 740 at [23].*

[435]. *Canon law is considered to be a foreign law and must be proven by expert evidence: McNally v Ireland [2009] IEHC 753 at [62], [2011] 4 IR 431 at 448, [2011] 1 ILRM 40 at 54.*

[436]. *McMahon v McDonald, unreported, High Court, 3 May 1988 at 29.*

[437]. *McMahon v McDonald, unreported, High Court, 3 May 1988 at 30.*

[438]. *See Unicredit Global Leasing Export GmbH v Business Aviation Limited [2019] IEHC 139 at [74], where McDonald J stated that, 'in any case to which foreign law applies, that law must be pleaded and proved as a fact to the satisfaction of the court by expert evidence.'*

[439]. *[2016] IEHC 597, [2016] 3 IR 384.*

[440]. The report also cited decisions from the United Kingdom, Australia, New Zealand and South Africa, and contained observations on Irish constitutional law. Counsel for the plaintiff pointed out that, were the report to be admitted, it would be open to the defendants to call counter-evidence from experts from the United States, the United Kingdom, Australia, New Zealand and South Africa. Kelly P considered that, in the conduct of a trial involving solely issues of Irish law, this would be absurd: [2016] IEHC 597 at [33], [2016] 3 IR 384 at 398. [It is a little difficult to see why it would necessarily be absurd if there was some learning to be gleaned from foreign law or if the court stood to be misled by what was stated as to foreign law].

[441]. [2016] IEHC 597 at [29]–[34], [2016] 3 IR 384 at 397–398. See also Friends of the Irish Environment v The Government of Ireland [2018] IEHC 740 at [23].

[442]. [1925] 1 IR 90.

[443]. [1925] 1 IR 90 at 112 (per Kennedy CJ). Cited with approval in O'Brien v Clerk of Dáil Eireann [2016] IEHC 597 at [26], [2016] 3 IR 384 at 397.

444. Walsh v National Irish Bank Ltd [2013] IESC 2 at [6.3].

[445]. In re Anderson, unreported, High Court, 6 July 1995; Baron de Bode's Case (1845) 8 QB 208; Attorney General v Dyer [2004] IESC 1 at [13], [2004] 1 IR 40 at 44. It is apparent from the decision in Dyer that it is sufficient if the person is a practitioner and he or she does not have to furnish evidence of any particular or special expertise.

[446]. Glentanar v Wellington [1947] Ch 506, [1947] 2 All ER 854.

[447]. Barford v Barford [1918] P 140 (witness had been called to the Bar in a number of countries and was entitled, as a matter of course, to be admitted to practise in the relevant jurisdiction).

[448]. O'Callaghan v O'Sullivan [1925] 1 IR 90 (one of the experts in Canon Law had acquired his expertise through study in Maynooth and Rome).

[449]. See Ajami v Comptroller of Customs [1954] 1 WLR 1405 (bank manager permitted to give evidence as to whether certain bank notes were legal tender); De Beéche v South American Stores [1935] AC 148, [1934] All ER 284 (evidence of banker admitted in relation to proper construction of contractual term); Vander Donckt v Thellusson (1849) 8 CB 812 (merchant who had carried on business in Belgium permitted to give evidence to prove the law in relation to the presentment of a promissory note).

[450]. ICDL v The European Computer Driving Licence Foundation Ltd [2012] IESC 55 at [107], [2012] 3 IR 327 at 362.

[451]. O'Callaghan v O'Sullivan [1925] 1 IR 90 at 119; Sussex Peerage Case (1844) 11 Cl & F 85 at 115; Baron de Bode's Case (1845) 8 QB 208 at 250.

[452]. Per Lord Brougham in the Sussex Peerage Case (1844) 11 Cl & F 85 at 115.

[453]. Earl Nelson v Lord Bridport (1845) 8 Beav 527.

[454]. O'Callaghan v O'Sullivan [1925] 1 IR 90 at 121; Earl Nelson v Lord Bridport (1845) 8 Beav 527.

[455]. McC v McC [1994] 1 IR 293; McNamara v Owners of S.S. Hatteras (No.2) [1933] IR 675 at 699-700; O'Callaghan v O'Sullivan [1925] 1 IR 90 at 121.

[456]. Bumper Development Corp. Ltd v Commissioner of Police [1991] 4 All ER 638; Duchess Di Sora v Phillips (1863) 10 HL Cas 624.

[457]. [1925] 1 IR 90 at 119. See also MacNamara v Owners of the SS 'Hatteras' [1933] IR 675 at 699 and Waterford Harbour Commissioners v British Railways Board [1979] ILRM 296 at 306.

[458]. MacNamara v Owners of the SS "Hatteras" [1933] IR 675 at 699.

[459]. See Kelly v Groupama [2012] IEHC 177 (where the assessment of damages in accordance with French law for personal injuries was considered).

[460]. Kelly v Groupama [2012] IEHC 177 at 699–700.

[461]. See M McC v J McC [1994] 1 IR 293 and HI v MG [1999] 2 ILRM 1, where this approach was applied. See also O'Brien v Clerk of Dáil Eireann [2016] IEHC 597 at [26], [2016] 3 IR 384 at 397 and Official Assignee in Bankruptcy in the Estate of Sean Dunne v Dunne [2018] IECA 7 at [17], where Hogan J stated: 'Where there is a dispute as to what the law is or where the foreign law is doubtful or even obscure on the point in question, the Irish court must ultimately adjudicate on that question and form a view as to what the foreign law provides, any uncertainties on this question notwithstanding. But it is clear that it does so qua finder of fact.'

[462]. [2019] IEHC 139 at [89].

[463]. Data Protection Commissioner v Facebook [2019] IESC 46 at [4.1]; Unicredit Global Leasing Export GmbH v Business Aviation Limited [2019] IEHC 139 at [74]; Official Assignee in Bankruptcy in the Estate of Sean Dunne v Dunne [2018] IECA 7 at [17]; Friends of the Irish Environment v The Government of Ireland [2018] IEHC 740 at [23]; O'Callaghan v O'Sullivan [1925] 1 IR 90 at 112; MacNamara v Owners of the SS "Hatteras" [1933] IR 675 at 698; Walsh v National Irish Bank Ltd

[2013] IESC 2 at [6.2]; McCaughey v Irish Bank Resolution Corporation [2013] IESC 17 at 45; Earl Nelson v Lord Bridport (1845) 8 Beav 527 at 536.

[464]. McCormick v Garnett (1854) 23 LJ Ch 777. Such a finding may, however, give rise to an issue estoppel in subsequent proceedings between the same parties: George v AVA Trade (EU) Ltd [2019] IEHC 187 at [81] et seq.

[465]. McCaughey v Irish Bank Resolution Corporation [2013] IESC 17 at [45]."

457. Having regard to all of the foregoing, it seems to me that the below propositions can be stated as to the receipt of evidence of foreign law in Irish court proceedings:

[1] The proper mode of proving a foreign law is not by showing a law-book to a court; for a court has not organs to know and to deal with the text of that law, and therefore requires the assistance of a lawyer who knows how to interpret it.

[2] A skilful and scientific man must state what the law is, but may refer to books and statutes to assist him in doing so.

[3] "*With foreign laws an English Judge cannot be familiar; there are many of which he must be totally ignorant: there is, in every case of foreign law, an absence of all the accumulated knowledge and ready associations which assist him in the consideration of that which is the English law, and of the manner in which it ought to be applied, in a given state of circumstances to which it is applicable. He is not only without the usual and necessary assistance afforded by the accumulated knowledge and able suggestions contained in the arguments which are addressed to him, but he is constantly liable to be misled by the erroneous suggestion of analogies which arise in his own mind, and are pressed upon him on all sides. These difficulties are obvious enough, even in cases in which he may have before him the very words of that which is proved to have been the law applicable to the events in question. Even if we suppose it to be proved, that the law has not been legislatively repealed or varied, and has not fallen into disuse, and that the words have been accurately translated, still the words require due construction, and the construction depends on the meaning of words to be considered with reference to other words not contained in the mere text of the law, and also with reference to the subject-matter, which is not insulated from all others. The construction may have been, probably has been, the subject of judicial decision: instead of one decision, there may have been a long succession of decisions, varying, more or less, from each other, and ultimately ending in that which alone ought to be applied in the particular case. The difficulty which arises under such circumstances is obviously very great; but it is vastly increased, when the law itself, or the form or collocation of words in which the law is expressed, has never been authoritatively expounded, but is to be discovered from decisions or usages, or from the opinions of unauthorised writers, who may have written much that is acknowledged to be existing law, and also, in the same books, much which is contrary to existing law. The decisions were subject to be, and may have been, altered by subsequent decision, and the precise application of them to the case in question, may only be ascertainable, by means of accurate historical and legal deduction from all that has passed in the Courts on the subject; and a Judge who seeks information as to a foreign law, has not, in himself, the means of distinguishing the correct from the incorrect proposition of a text writer. Whoever has considered the nature of the difficulties which frequently arise in our own Courts, in the investigation of English law applicable to particular cases, and the mode of reasoning and investigation by which it is endeavoured to surmount those difficulties, will perceive what presumption it would often, nay generally, be, in an*

English Judge to attempt to apply the same process to the investigation of a foreign law, and the consideration of its proper application to particular cases. The rule of English law, that no knowledge of foreign law is to be imputed to an English Judge sitting in a Court of only English jurisdiction, is undoubtedly well founded. And as cases arise, in which the rights of parties litigating in English Courts cannot be determined, without ascertaining, to some extent, what is the foreign law applicable in such cases, the foreign law and its application, like any other results of knowledge and experience in matters of which no knowledge is imputed to the Judge, must be proved, as facts are proved, by appropriate evidence, i.e., by properly qualified witnesses, or by witnesses who can state, from their own knowledge and experience, gained by study and practice, not only what are the words in which the law is expressed, but, also, what is the proper interpretation of those words, and the legal meaning and effect of them as applied to the case in question".

[Subject to substituting the word ""Irish"" for "*English*" in the above quote the same observations apply as regards Ireland].

[4] Roman Catholic canon law is foreign law which must be proved as a fact and by the testimony of expert witnesses according to the well-settled rules as to proof of foreign law.

[5] The opinions of persons of science must be received as to the facts of their science. That rule applies to the evidence of legal men; and it is not confined to unwritten law, but extends also to the written laws which such men are bound to know.

[6] Properly speaking, the nature of such evidence is, not to set forth the contents of the written law, but its effect and the state of law resulting from it. The mere contents indeed might often mislead persons not familiar with the particular system of law: the witness is called upon to state what law results from the instrument.

[7] If an expert in the law of a foreign country, whose qualifications and credibility are unimpeached, gives evidence upon oath that the law of that country is so, or that a particular contract, or clause in a contract, is, or is not, valid according to the law as administered in the courts of that country, and his testimony is not contradicted by the evidence of another expert, or broken down by cross-examination, the Court which has to decide the question is just as much bound to accept and act upon that evidence as it would be to accept and act upon the evidence of any credible and uncontradicted witness upon any other question of fact or opinion. *Oportet discentem credere* ('the learner must believe').

[8] The court cannot reject the evidence of the expert because it would itself have come to a different conclusion on perusal of the text of the foreign law or on consideration of the terms of the document which is to be interpreted or whose validity is to be decided in accordance with that law.

[9] Where there is a dispute as to what the law is or where the foreign law is doubtful or even obscure on the point in question, the Irish court must ultimately adjudicate on that question and form a view as to what the foreign law provides, any uncertainties on this question notwithstanding. But it is clear that it does so qua finder of fact."

[10] In the ordinary way, foreign law is treated as a matter of fact to be established, in the Irish courts, by way of sworn evidence of that fact.

[11] An affidavit from an appropriately qualified lawyer is the normal way in which evidence as to foreign law is to be established.

[12] A party who wishes to dispute such evidence is required to put forward its own contrary evidence from a likewise suitably qualified lawyer.

[13] In the case of a dispute, then it may well be necessary that both lawyers be cross-examined so as to assist the Irish court in coming to a conclusion.

[14] Reference to case law or other materials from foreign jurisdictions is not an appropriate way, in the absence of evidence from a suitably qualified lawyer making reference to such materials, to establish the law concerned.

[15] Irish courts may have occasion to consider the case law of other jurisdictions which may provide persuasive authority as to the proper approach to be adopted in like circumstances in Ireland. However, when so doing the Irish courts are simply referring to materials which may be of assistance in interpreting Irish law.

[16] Where an Irish court is required, for the purposes of determining the proper result of litigation, to reach a conclusion as to relevant foreign law, then such a conclusion cannot be reached simply on the basis of counsel referring the Irish court to statute or case law from the relevant jurisdiction.

[17] Expert evidence is not admissible in respect of any matter of domestic law.

[18] Expert evidence is not only admissible but is mandatory in respect of matters of foreign law, which is required to be proved as a fact.

[19] The evidence of a non-expert as to a foreign law is inadmissible.

[20] In general, the dividing line between domestic law and foreign law is straightforward but it should be noted that, where the construction or application of legislation that is common to both Ireland and England arises in the context of a question of English law, this will be considered to be an issue of foreign law.

[21] Where the interpretation and application in another jurisdiction of a convention that has been incorporated into domestic law arises, this again is considered to be a question of foreign law.

[22] In order for evidence of foreign law to be admissible, an issue of the foreign law in question must arise for determination in the proceedings.

[23] While the decisions of the courts of other states may be cited before the Irish courts as persuasive authority, expert evidence of foreign law is not admissible for this purpose.

[24] It is ultimately a question of fact as to whether a person has sufficient expertise in a foreign law but it is likely that a person will have the requisite expertise if he or she is a practitioner, a former practitioner, or a person qualified to practise in the particular foreign jurisdiction, or is person who, though unqualified, has acquired sufficient expertise by academic study or, in matters of commerce, by practical experience.

[25] Regardless of how the witness has acquired his or her expertise, she should be an independent expert.

[26] A judge is generally not permitted to consult the sources used by the expert, but she may do so when the evidence given is unclear or where there is a conflict between the experts.

[27] In no circumstances may the judge go beyond the sources used by the expert and conduct her own research into foreign law.

[28] Where the expert evidence establishes that a discretion is enjoyed by a court under the foreign law, an Irish judge will not necessarily be bound by the view of an expert as to how that discretion should be exercised.

[29] Ordinarily, a court would find it difficult to resolve a dispute between experts as to foreign law without cross-examination of the experts.

[30] As an issue of foreign law is regarded as a matter of fact the finding of a court on the issue has no precedential value and if the point arises again, it must be decided anew by reference to fresh expert evidence.

[31] It follows that the determination of a trial judge on an issue of foreign law is

regarded as a finding of primary fact for the purposes of any appeal from that determination.

16

The Evidence of Professor Thomas

A. Introduction

458. Professor Thomas is a professor of law at Georgetown University and has a longstanding expertise in patent law. Subject to para.4 of this judgment, an abridged version of his reports is attached hereto as Appendix 14. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

459. In his first statement, Prof. Thomas states as follows:

> "*I have been contacted by solicitors acting for Norton (Waterford) Limited trading as Teva…to provide assistance as an independent expert on US federal law in patent proceedings in several jurisdictions in Europe. I have been informed that there are patent proceedings brought by Teva and its relevant entities within the Teva Group against BMS Holdings Ireland Unlimited Company…and its relevant entities within the BMS group in relation to a patent covering the product, Apixaban, across various jurisdictions in Europe*",
>
> and (at §40), he states:
>
> "*I have had the opportunity to review the Holland Report which I understand was relied upon by BMS Ireland in the Italian proceedings. While I have the greatest respect for the late Justice Holland, I strenuously disagree with his conclusion...*",
>
> and in his second statement (at §2), he states:
>
> "*I have been provided with, and had the opportunity to review, the Statement of Professor Donald Chisum dated 13 May 2022 (the 'Chisum Statement'). My review of the Chisum Statement confirms my earlier opinion...*".

B. Examination

1. Federal Law and Patent Law

460. Asked how the patent law system operates in the United States and the scope of federal law in the patent law area, Prof. Thomas answered as follows:

> "[T]*he United States has had a patent system continuously since its founding. It's mentioned in the Constitution*….[T]*here's one federal agency, the US Patent and Trademark Office*….[T]*hat is the agency that handles acquisition of patent rights. The federal patent law controls…acquisition, enforcement and transactions in patents*….*It is known as the Patent Act. It resides in Title 35 of the US Code. It's...been recently amended on a significant level by the American Invents Act*….[The most significant provision for this case]….*is §261*….[It] *is entitled 'assignments/ownership'*….[a]*nd it imposes a requirement of writing. So, under federal law, to assign a patent, it must be in a written instrument.*"

461. On a related note, later in the course of examination, counsel noted that it is the United States, not Delaware that is a party to the Paris Convention and asked what significance that has in terms of whether the appropriate framework for determining who is to be regarded as a successor in title

is Delaware law or federal law. To this, Prof. Thomas responded as follows:

> "*It's a pretty significant point. As you might imagine, it is the federal government of the United States that has the ability to enter into international agreements on behalf of the nation. The State of Delaware could not enter into an international agreement permissibly with Ireland. So, the key is that we are looking to federal law because the federal law is the one that's going to reflect the commitment of the United States to the Paris Convention.*"

462. Reminded later of his conclusion in his written statement that "*For the most part, state contract law governs the ownership issues resulting from assignments*", Prof. Thomas confirmed that this is how he views the demarcation between the federal and state zones of application to operate.

2. Section 261

463. Asked to provide more detail about §261, Prof. Thomas indicated as follows:

> "*Section 261* [requires]*…an assignment in writing. So, if you want to transfer title from the predecessor to a successor, it has to be in a written instrument. It also sets out a race notice recording statute. So, if someone sells the patent to different parties, the first party has three months to register it with the agency. Otherwise then whoever registers first with the agency gets the patent and the other one's left with a breach of contract suit….*[S]*ometimes the federal statute permits the use of state law. And a principal way to do that would be the interpretation of a patent licence, or assignment really, patent assignment. So, Section 261 obliges a written instrument with sufficient words of conveyance to have an assignor and assignee. At that point, further interpretation of the contract would be a matter of state law. So, for example, has there been a breach? Suppose the contract, the assignment does not identify the patent by number, it might say any patent relating to project X. So, that issue might start getting into state law a little bit more…..*[O]*nce there is an assignment, with…words of conveyance, there* [are]*…no magic words. The law is relatively lenient, once there is a written assignment.*"

464. Asked at a later stage in the course of examination whether §261 applies to an assignment in law, Prof. Thomas indicated that "*That's what the statute says. It speaks to 'in law'….The statute does not speak to equitable assignments.*"

465. Still later in the course of his examination Prof. Thomas noted Prof. Chisum's view (of which more later below) that §261 somehow relates to standing to sue in Federal Court, then observed as follows:

> "*I vehemently disagree with that and can state with a great deal of firmness that §261 doesn't say anything about any court. It is titled 'Ownership assignment' without qualification. You don't have standing to sue on a patent application. So, it speaks to patent applications. That's not an enforceable interest. This is an ecumenical requirement in US law, it's not limited to standing cases. And I would say the US PTO requires a chain of title in writing in order to qualify that applicant as having the right to act before the agency.*"

3. Sufficiency of Words of Assignment

466. Asked whether, in determining the sufficiency of the words of assignment, it is federal law or state law that governs, Prof Thomas indicated as follows:

"*There'd have to be an assignment, so that would be federal law. There'd have to be something that's saying I'm not licensing it to you, this isn't a security interest, this is not transferring title to you. That's federal law…..the Federal Patent Act.*"

4. Assignments of 2001 and 2007

467. Asked whether the wording of the assignments of 2001 and 2007 was standard, Prof. Thomas indicated that they were standard form assignments.

5. Assignments and Priority Rights

468. Asked what happens as regards the priority right when a patent is assigned, Prof. Thomas indicated as follows:

"[T]*he most common form of assignment, if I simply assign a patent to you with a very short, even one or two sentences; that would convey the priority right as well. Of course, I could specifically say I'm going to have the US patent law sign the European interest to an Irish firm, that can be done through specific covenants. But normally, you just transfer the patent…*[and] *the priority right comes part and parcel with it.*"

6. Corporate Separateness

469. Asked whether (1) there is a principle of corporate law enshrined in the federal system that might be relevant to the issues being considered in these proceedings and (2) there is any difference between federal law and state law in this regard, Prof. Thomas indicated as follows:

"[A]*n axiomatic principle of the law in the United States is that corporations are separate persons, they are not to be conflated, even if there's some sort of ownership. So, that's quite fundamental and it's recognised across the country….It's a universal principle in the United States….In terms of asset ownership, each enterprise, each corporation owns its own assets and there's no ownership interest of other assets, even from a parent corporation.*"

470. Later in his examination, counsel for Teva brought Prof. Thomas to a number of US cases pertaining to corporate separateness, *viz*.:

– *Maquet Cardiovascular LLC* v. *Abiomed* 2018 WL 4211364 (US District Court, Mass.).

  Led by counsel to p.3 of the judgment and specifically the observation that "*Common corporate structure does not overcome the requirement that even between a parent and a subsidiary, an appropriate written assignment is necessary to transfer legal title from one to the other."* Abraxis Bioscience, Inc. v. Navinta LLC*, 625 F.3d 1359, 1366 (Fed. Cir. 2010)*", Prof. Thomas noted that "[T]*he statement is quite clear; a common corporate structure does not override statutory commandment without a written assignment from one party to the next. And I think the policy reasons are set out very smartly on page 441*". His attention drawn, in particular, to the observation that "*The Court is wary of extending the doctrine of equitable title"*, Prof. Thomas attached the following significance to this observation:

  "*So, we're talking about equity - so, you know, the notion that, hey, there's an employee who has agreed to assign her rights and hasn't done it because of time-limited rights, we should allow that implied-in-fact contract. But as the Court says, there's nothing*

unfair about a company incorporating a subsidiary. That's a deliberate choice and there's not a matter of the intervention of, you know, equitable concerns. So I think the court rightly sets out some significant policy concerns."

– *Buechner* v. *Farbenfabriken Bayer Aktiengesellschaft,* 154 A.2d 684, 686-87 (Del. Ch. 1959).

Responding to counsel's noting that this was a decision of the Supreme Court of Delaware in which the court says that companies have a separate existence and that shareholders of one corporation do not transfer equitable title to another separately held corporation, Professor Thomas indicated that he had not detected any difference in principle between this Delaware decision and the federal decisions to which he makes reference in his report. Pressed further on the considerations that arise for a company as to where to place a patent within a group of companies, Prof. Thomas indicated as follows:

"[I]*n US law, remedies depend a lot on* [who is]*...the patent proprietor….*[T]*he fundamental remedy for patent infringement is the lost profits of the patent proprietor. The case law makes quite clear that the patent proprietor, even in a group or commonly owned companies, the patent proprietor, that's the one whose lost profits we're talking about. In addition, to obtain an injunction, the Court will look to the position of that particular patent proprietor – for example, is that patent proprietor engaged in direct competition with the adjudicated infringer? And they will make that decision before issuing the injunction. So, it's very well established law that remedies are based on the specific corporation that is the proprietor of the patent and not what's going on with other members of a group of companies.*"

Professor Thomas further indicated in this regard that it is "*essential*" to formalise and make clear where ownership lies. And in response to a question from counsel he indicated that if there is a challenge to standing that requires evidence to be adduced to demonstrate the necessary standing.

– *Hologic, Inc.* v. *Minerva Surgical, Inc.* 163 F. Supp. 3d 118 (D. Del. 2016).

Noting that this was a decision of the Federal District Court in Delaware in which the court indicated that there was complete control and, therefore, they were going to accept it for standing purposes, counsel for Teva asked how Prof. Thomas saw this case fitting with the other authorities that he had referred in terms of the separateness between the parent and the subsidiary. In his answer, Prof. Thomas indicated as follows:

"[W]*hat's interesting to me…is the authority that the court cites. So you can see it cites Top Victory, which is a case from the Northern District of California, a federal case. And…it cites the Southern District of New York, the Federal Court of first instance in Manhattan, another case from the Northern District of California and then the Southern District of Texas. All federal cases. Here, the Court holds – and there's not many of these cases; in fact I am not sure there's any other cases that I can recall right now – but here the court says 'We're going to essentially pierce the corporate veil'; they're saying that one corporation is so*

> *aligned with the other that it will, in a sense, disregard corporate separateness for this case. So, this would essentially be a question of fact: Is there some sort of ability to breach the corporate veil? That's quite rare in the United States, usually involving matters of fraud. And I don't think those are the facts here.*"

– *Email Link Corp* v. *Treasure Island LLC, 2012 WL 4482576* (D. Nev. 25 Sept. 2012)

Responding to counsel's noting the following segment of the judgment in this case.

> "*Specifically in the patent context, the Federal Circuit has applied this basic principle of American corporate law to hold that once a parent company assigned a patent to its subsidiary, the parent no longer had rights in the patent, even though it controlled the subsidiary*",

Prof. Thomas observed as follows,

> "[T]*hat's correct. And in this opinion, Judge Reed speaks, you know, quite clearly and bluntly. If you look at the left column on page 379, he says, 'That is, of course, the whole point of a corporation, to isolate its assets, liabilities, and operations' and that applies with equal force to patents.*"

7. *Digitech*
(*Digitech Image Techs LLC* v. *Newegg Inc*., 2013 WL 1871513 (C.D. Cal. 2013))

471. Asked about the *Digitech* case, Prof Thomas indicated as follows:

> "*The key language there is, of course, that a corporate parent does not possess equitable title in the subsidiary's patents. That's the authority that's been presented to this court. And there's no contrary authority in this litigation….The court* [also] *correctly states that patent rights are acquired and transacted, in keeping with federal law.*"

8. Different Concepts of Equitable Title

472. Noting that Prof. Chisum suggests there to be a different concept of equitable title as regards (i) federal rules governing standing and (ii) in terms of understanding ownership or how ownership is disposed of in United States law, Prof. Thomas indicated as follows:

> "*With respect to Prof. Chisum, we have equitable title for standing and for all other purposes. There's not one ownership doctrine for one purpose and another ownership doctrine for another. The Court, when it addresses standing issues, is looking at lots of factors….*[*e.g.,*] *is the case ripe? is it amenable to a remedy the court can issue? And of course part of it is you want to have the right moving party….[S]o equitable title has to deal with that….*[E]*quitable title is a standalone doctrine and it applies across the board*."

473. Asked later whether there is any principle of patent law which says "[Y]*ou can be the equitable owner of a patent for patent law purposes, but for all other purposes – revenue purposes, liability purposes etc. – you ignore the equitable ownership?*", Prof. Thomas gave a three-word answer: "*Absolutely not, no*".

9. The Decision in *Beam Laser*

474. Asked about the decision in *Beam Laser*, Prof. Thomas drew my especial attention to the observation therein (at 126) that *"Ownership of corporate stock does not create equitable title in that corporation's property*" and to footnote 6 (at 521) wherein it is stated that "*The only cases from the Federal Circuit recognizing an equitable title to a patent, of which the court is aware*" – and Prof. Thomas confirmed that this awareness is complete "*involve a contractual relationship*". Professor Thomas added at this point that "*That's where equitable title comes up. That is the only time it's recognised in this context.*"

10. Employer/Employee Cases

475. Asked to expand on the operation of equitable title in the employer/employee context, Prof. Thomas observed as follows:

> "*We do not have, in the United States, a statute dealing with employed inventors, so we do it as a matter of federal common law, essentially, or it could be State common law. And that is an implied concept theory….the concept being that when an employer has set up a laboratory, supplied equipment, directed the employee, paid a salary, then that inventive work product would then belong not to the employee, but to the employer. If the employee is uncooperative, the employer may compel a transfer of title from the employee to the employer. In a sense, that's what equitable title gives you, it gives you the ability to demand an equal title….*[T]*his is the only time we have equitable title in the US with respect to the issues we're discussing here. It is a contract. There is also a statute I would like to draw the Court's attention to, §118. So, as we have already heard, in the United States to file a patent application you have to be the inventor, so the natural person who developed the invention. And there has to be a chain of title from that inventor to someone who chooses to apply later. Obviously, patents are very time-sensitive rights, so Congress a gave some relief in this respect and it did so in §118….*[It] *says that if someone has assigned in writing, agreed to assign in writing, or there's a sufficient proprietary interest in the matter – and that phrase could be what we might say is equitable title. If, and only if, an inventor is uncooperative or unavailable, then that person, that title, the equitable titleholder may file a patent application on behalf of the inventor, and that's intended…to make sure that rights aren't lost by public uses or sales. That patent would issue in the name of the inventor. And so the employer or whomever else would have to compel transfer, typically by going to court.*"

Reference was also made in this context to *Hewett* v. *Samonsite Corp.*, a Colorado state law case as an example of a dispute between the employers and employees as to ownership.

11. Legal/Equitable Title

476. Asked about how often he had seen assignments within corporate groups whereby the equitable title is assigned to one company and the legal title to another, Prof. Thomas observed as follows:

> "*Let me say first through my experience with US PTO, also before I joined the Academy, really all throughout the latter half of my university years in law school and beyond I was actually drafting patent applications and interacting with the US PTO as a patent attorney. There will always be a chain of title. You have to have a documented title from the inventor to whoever the applicant is. So, it's of course ubiquitous to have companies assign each other inventions. Because again, they are separate persons.*"

477. I would respectfully note that while this was a customarily informative answer it did not actually appear to answer the question posed.

12. Recording of Assignments

478. Asked whether there is a system of recording assignments at the US PTO, Prof Thomas observed as follows:

> "[T]*he US PTO maintains a registry of assignments….The advantage to the patent proprietor is…it puts the world on notice of the patent. And again it is a race notice system….And of course, the public has a right to know who owns the patent, because they're very valuable rights, they have a great impact, for example, in this case, on public health*."

13. The Email of 24th October

479. Asked about the reference in this email to "[m]*aintain*[ing] *legal ownership in Bristol-Myers Squibb*", and, in particular, on the meaning of the term "*legal ownership*", Prof. Thomas stated as follows:

> "*The term 'legal', I think, in this sense just refers generally to the entire patent. There's not a crisp technical meaning, it's just saying that legally, as a matter of law, we're going to assign patents here....*[I]*f you were going to speak to beneficial interest or equitable title or whatever you want to call it, that would be spelled out explicitly. So that's the meaning I get from this e-mail.*"

480. Asked whether the email would satisfy the requirements of §261, Prof Thomas indicated as follows:

> "*It would not. Because* [there are]*...no sufficient words of conveyance and there is no assignor and assignee...there's no transfer. And back to US PTO practice, it's the Office of Patent Application processing...that would handle these sorts of documents. There's no way the Patent Office of the United States is going to register an e-mail like this as some sort of evidence of an assignment. It just, it would be refused. It just would not suffice....*[Y]*ou could have an e-mail assignment. It may not reflect best practices, but it would be effective. But again, you'd have to have words of conveyance from one party to the next. And that does not appear here....Given* [that BMS is]*...a multinational firm, and...a US firm, respectfully, to my fellow Americans, they should be familiar with US law and US PTO practices.*"

14. The BMS Manual

481. Turning to the manual and asked:

- what he understood the reference to an "*assignment*" on p.169 of the manual to be, Prof. Thomas responded that he "*would understand that to be a written assignment conveying title from one party to the other*".
- what he understood the reference to title in this context to be, Prof. Thomas responded that "*It would be both legal and beneficial title. It's the entire ownership.*"
- about the process in the United States whereby one may make a provisional filing, Prof. Thomas indicated as follows:

> "[I]*t actually has to be a complete, full application. The US PTO does not put it into queue for examination, but it can be*

> *relied upon – up to 12 months later you can claim domestic priority. It's supposed to put to US inventors on an even footing with our foreign counterparts, because you would have one year here filing in the European Patent Office, then file at US PTO, this allows US domestic inventors also to essentially get that extra year before they move forward. That's a provisional application....You would file a non-provisional application within 12 months....* [T]*he specification would have to be the same. So you couldn't add any subject matter, that would get rid of what you call fair basis and we call written description. But you could add more claims, that is for sure.*"

482. (On a related note Prof. Thomas confirmed that, as is noted in the manual, a provisional application alone cannot result in a patent.)

15. BMS Policy

483. Asked about the BMS policy and the reference to legal entity registration, Prof. Thomas indicated as follows:

> "*With respect to* [BMS]...*I'm not sure what the policy is. I wasn't clear what the policy was. And the US PTO is not going to register a policy. Aspirational statements of what we ought to do simply doesn't act as an assignment and it's not something the US PTO would respect.* [As to the meaning of the words 'legal entity registration']...[t]*hat would be a matter, I believe, of state law incorporating or otherwise having* [an]*...address...or some registration in a state – and by 'state' I mean California, New York, that sort of thing.*"

16. *Fujifilm*

484. In *Fujifilm*, Profs. Thomas and Chisum previously found themselves on opposite sides in proceedings in which there was an issue as to whether there was a beneficial ownership transfer sufficient to make somebody a successor in title under the laws of Delaware. The court in that case held there was a sufficient transfer of beneficial title. Asked whether he could identify, by reference to the principal facts of *Fujifilm* any difference between that case and the present proceedings, Prof. Thomas indicated as follows:

> "*I must say at the outset I was unsuccessful in my opinion, my evidence was not accepted by Justice Henry Carr. But I think Justice Carr was largely persuaded to uphold priority....And so, if you look at paragraph 6...it reads 'Upon request of BASF I will execute such (a) patent applications... and (b) all other documents deemed necessary by BASF to transfer to BASF...' – and here's the key language, your Honour, '...its nominees or assigns.' So...my reading of this case was that Justice Carr was persuaded, under that particular agreement, that BASF could nominate someone and preserve a chain of title through that route. I'd also note [that] there was a bit more documentary evidence and ultimately – this was a matter of German corporate law, of which I do not have particular expertise – I think the court was persuaded, under that EISA and the German law.*"

17. Section 118

485. Section 118 of the federal patent law (35 U.S.C.) ("*Filing by other than inventor*") provides as follows:

> "*A person to whom the inventor has assigned or is under an obligation to assign the*

invention may make an application for patent. A person who otherwise shows sufficient proprietary interest in the matter may make an application for patent on behalf of and as agent for the inventor on proof of the pertinent facts and a showing that such action is appropriate to preserve the rights of the parties. If the Director grants a patent on an application filed under this section by a person other than the inventor, the patent shall be granted to the real party in interest and upon such notice to the inventor as the Director considers to be sufficient."

486. Asked to speak as to §118, Prof. Thomas observed, amongst other matters, as follows:

"*Section 118 discusses, in a sense, standing to file a patent application....You may be familiar, your Honour, with the issue, or the topic of assignee filing. So it's long been the practice here in Europe that the assignee, the employer for example, could file a patent application on its own behalf and prosecute that application. The United States, until recently, had a great deal of emphasis upon the natural person, the inventor. So we did not allow assignee filing. Ultimately, and with the America Invents Act in 2011, we relented; we thought the European practice represented the best practice, so we adopted it for ourselves. So, Section 118, the version you see here, does seem to afford a broader capacity for corporations to file if they have some sort of equitable interest on behalf of the other. But the predecessor version is much more constrained, it applies again only when the inventor is unavailable or recalcitrant. So, that statute shows that Congress wanted a chain of title from the inventor, except in these very narrowly cabined situations.... So, again, if you look at this version of Section 118, I mean, look at the wording...it says first: 'A person to whom the inventor has assigned or is under an obligation to assign the invention may make an application for patent.' Then it says a person who otherwise shows proprietary interest in the matter, essentially, may also make an application for a patent, but as an agent for the inventor. So, this allows assignee filing. And it seems to essentially broaden the array of standing, who can actually file a patent application on an invention. In this case, we are not under this statute, we are under an earlier statute which limits standing to file a patent application to just really these two narrow cases. Otherwise, you always have to have – you start with the inventor and you have to have a chain of title. That way, you have ownership and you establish the right to act of the agency.*"

487. When counsel for Teva put it to Prof Thomas that under the original §118, if the owner would not cooperate or could not be found, the assignee could apply rather than the inventor. The original §118 provided as follows:

"*Whenever an inventor refuses to execute an application for patent, or cannot be found or reached after diligent effort, a person to whom the inventor has assigned or agreed in writing to assign the invention or who otherwise shows sufficient proprietary interest in the matter justifying such action, may make application for patent on behalf of and as agent for the inventor on proof of the pertinent facts and a showing that such action is necessary to preserve the rights of the parties or to prevent irreparable damage; and the Commissioner may grant a patent to such inventor upon such notice to him as the Commissioner deems sufficient, and on compliance with such regulations as he prescribes*."

488. Professor Thomas responded to counsel's question as follows:

"*Yeah, the assignee could apply – again, just in those two cases. And it also said when there's someone who has a sufficient proprietary interest. Again, the three categories were agreed in writing to assign, had assigned in writing or, again, there was a sufficient proprietary interest. And the point of this, just to cut to the chase, Congress enacted a statute that restricted, in a sense, standing to file to those cases. So, you*

can't argue there that there's this broader equitable interest in allowing others to file. And that's significant, because, you know, here we have a break in that chain of title. I would say, you know, we spent a lot of time on this. Coming out with assignee filing took years. And I really feel sorry for myself, the American Intellectual Property Law Association, the American Bar Association, if all along anyone who could claim some sort of beneficial interest somehow could've filed anyway. You know, that's just not the sense of Congress. And I say that with quite a bit of conviction."

489. Reminded in this context of his observation in his written statement that:

"*This uniform approach makes sense as a matter of innovation policy, for it makes little sense to have ownership of a particular invention, patent application, or patent depend upon which doctrine is being applied. To put the matter squarely, in the US at least, one person cannot be the owner of an invention, patent application, or patent with respect to one legal issue, while a different person owns it for another*",

Prof. Thomas stood by this observation, remarking that:

"*Having an orderly chain of title for proprietary rights is important to patents as a fundamental policy goal. You don't have one owner in the United States for one purpose and another owner for another purpose. Equitable title concepts are universal and...don't differ based on the legal context in which they might be asserted*."

18. *Dalzell*

490. Counsel for Teva noted that Prof. Chisum places "*a lot of emphasis*" on the decision of the US Supreme Court in *Dalzell* (a case which pertains to equitable assignment in the context of an employer-employee agreement for the sale and assignment of a right). Asked to comment on *Dalzell*, Prof. Thomas observed as follows:

"*Dalzell dates from 1893. First, I'd say I have no problem with the holding of this case, properly understood. This case, by the way, it's never been cited by the Federal Circuit....*[b]*ut I think for what it says, it's appropriate law. Here, we have an employee, Dalzell, who was hired by Deuber to create an invention, and he did so. And then, of course, he didn't assign the invention to his former employer, with which he had had a falling out. The holding in the case – and let me see if I can find the precise language here...here it is, it's on page 15 of 462* [p 320 of judgment]....*[a]nd let's just read it:*

'An oral agreement for the sale and assignment of the right to obtain a patent for an invention is not within the statute of frauds, nor within' – what is now Section 261 of the Patent Act – 'requiring assignments of patents to be in writing, and may be specifically enforced in equity, upon sufficient proof thereof.'

It was and remains the law that if someone has orally agreed to assign in the future – this would be an executory promise, it would have to be consummated later – then that can be upheld. My issue is I just don't see how that's relevant to the facts of this case....And, you know, actually, if you read this case, the argument didn't work; the court said there's not a sufficient demonstration of equitable factors saying that there was such an agreement. That's what the Supreme Court concludes. But...again, I don't have any particular issue with the fact that an oral agreement could be made in an executory way to assign in the future. I just don't see any such oral agreement here. There's been no evidence of any oral agreement. So I just don't know [why]*...this is being...given such importance.*"

491. Reminded that *Dalzell* does not address the doctrine of corporate separateness and how that would interact with the existence or otherwise of any equitable title, Prof Thomas responded:

> "[T]*hat's absolutely correct. This is from a simpler time and, you know, between a former employee and the employer, this isn't multiple corporations.*"

19. *Hewett* (a.k.a. *Samsonite*)

492. Prof. Thomas indicated in his second witness statement that "*Hewett correctly reflects US law, particularly as it applies §261 to an ownership dispute without regard to the law of standing; and also in its insistence that the ownership of patent rights must be expressly transferred in an unambiguous manner.*"

C. Cross-Examination

1. State and Federal Law and *Erie Railroad Co.* v. *Tompkins*

493. Asked about the demarcation between state law and federal law, Prof. Thomas indicated that "*a federal Court would apply state law when that's the governing body of law*." Brought to the section in *Erie* where Brandeis J. observes that:

> "*Except in matters governed by the Federal Constitution or by Acts of Congress, the law to be applied in any case is the law of the State. And whether the law of the State shall be declared by its Legislature in a statute or by its highest court in a decision is not a matter of federal concern. There is no federal general common law, Congress has no power to declare substantive rules of common law applicable in a State whether they be local in their nature or 'general', be they commercial law or a part of the law of torts. And no clause-in the Constitution purports to confer such a power upon the federal courts*",

Prof Thomas emphasised the opening caveat – "*Except in matters governed by the Federal Constitution or by Acts of Congress*" – and then moved on to observe that "[T]*he patent system is laid out in our original Constitution, it's not the subject of an amendment, it was put in initially. And of course, the Patent Act is an Act of Congress. So, because it's a matter of federal interest, you look only to state law where the Federal Patent Statute essentially allows it. So, that's the essential distinction...this first phrase.*"

494. Taken to the section in his first report where he observes that,

> "*In the US, state law governs the ownership of property (including intellectual property) and the interpretation of contracts. Therefore, the question of who has legal title to a patent is a matter of state law*",

and asked whether he was saying in this that the general principles of ownership of intellectual property are governed by state law, Prof. Thomas responded as follows:

> "[J]*ust to be absolutely clear, when I say ownership of property 'and' the interpretation of contracts, I mean that in a conjunctive sense, I don't mean that 'and' means 'or'. I'm saying when there is a contract to be interpreted, that that will dictate ownership. But again, I'm speaking here of a contractual matter, not a broad invitation to invoke state law....Section 261...says assignments have to be in writing....[a]nd that is the principal mechanism by which title to a patent is transferred from a predecessor to a successor. And of course, that's a matter of federal law. So it's the Federal Patent Act that explains how to assign a patent.*"

2. Section 261

i. Requirements of §261

495. Turning to §261, in particular the element thereof that states "*Applications for patent/patents or any interest therein shall be assignable in law by an instrument in writing*," counsel for BMS pointed to Prof. Thomas's assertion in his report that that is a minimal requirement, with Prof. Thomas responding as follows:

> "*I...observe the first word in §261 is 'Ownership'* [– this is in the title to the provision –]....[b]*ut...once there is an assignment in writing, there's fairly minimal requirements to what that writing has to actually say. It can't be a licence...there has to be an actual transfer....But again, no special words have to be used, but there has to be a covenant that transfers rights.*"

496. When counsel suggested that §261 "*doesn't govern any question of substantive ownership*", Prof. Thomas responded that "*It certainly does govern questions of substantive ownership. Because without an assignment in writing, you don't have a transfer*", an exchange that led counsel to embark upon a consideration of the decision of *Schwendimann v. Arkwright Advanced Coating.* Responding to the suggestion that *Schwendimann* is authority for the proposition that §261 imposes no form or content requirements at all, that it requires merely that an assignment be documented in an instrument in writing, Prof. Thomas observed:

> "*It's plain on the wording of the opinion* [which states "*In addition to the §261 written... requirement*"] *that the predicate is to have a written assignment. And again, in writing, covenant with words of conveyance. At that point, other interpretive issues would fall to the state law....I think it's important to note in this kind of standing case that the court is focusing its discussion upon that issue, it's not writing a generalised treatise about other applications of §261....I'm wary of taking language out of context or trying to draw broad general principles. We're common lawyers, we resolve the case in front of us. Section 261 is not a formal requirement, in that it's just for show, it's not limited to standing, it's a requirement that is universal across the United States....I seem to be a loggerheads with counsel about not reading the first sentence in the right column on page 447, which says 'In addition to the §261 written instrument requirement'; that phrase can't be read out of the opinion. Also, counsel has quoted from the Jim Arnold opinion* [*i.e. Jim Arnold Corp v Hydrotech Systems Inc,* 109 F.3d 1567, 1571 (Fed. Cir.1997)]. *I invite the Court to review the opinion. I think you'll find it very straightforward. If you just read the first sentence of Jim Arnold, what you're going to say is this is a jurisdictional matter....They're just saying 'Look, if this is a contract case involving whether something was transferred or not, that's going to go into the state courts'. It doesn't say that state courts means you don't apply federal law and the requirement of an instrument in writing.*"

497. Counsel pressed Prof. Thomas on this aspect of matters, leading to the following exchange:

Counsel:	*...I have to put it to you that it's not a question of jurisdiction, it is a question of the application of substantive law....*[I]*f you turn to page 450 of the report, you will see that* Enovsys*...is referred to again, as well as* Larson -*v*- Correct Craft*, and it says: 'Holding that 'questions of patent ownership are determined by state law'"....''*
Prof. Thomas:	*Again, subject to the requirement of §261. There has to be a writing.*
Counsel:	*There has to be a writing for an assignment of the legal interest?*
Prof. Thomas:	*Yes, there has to be a writing for an assignment of a legal interest.*

Counsel: ...[But] Schwendimann *is saying...legal title is a question of state law.*

Prof. Thomas: *Again...*Schwendimann*...like all the others that actually recognise any equitable interest, is a contract case....*[A]*gain, we're common lawyers; statements are made in the context of a specific dispute and here it's a contract case. I don't think there's any question for anyone in this room that §261 imposes a requirement of a written instrument for an assignment. This is not a broad invitation to invoke any beneficial interest of state law that might ever be created....state law covers the interpretation of contracts once there is a written assignment. And the...effect of that contract might be to convey ownership. And that's a distinction, I think, that's quite significant.*"

498. At no point did Prof. Thomas depart from his view, which at a later point in his evidence, he simply and clearly stated in the following terms:

> "*§261 requires that a patent assignment be in writing. So, that's really two requirements. One is that it's a written instrument and the other that there is a covenant with sufficient language of conveyance. So, we know that's an assignment. At that point then you would look to state law for the remainder of the interpretation of the contract....Because the federal statute requires an assignment in writing, first we have to figure out is this writing an assignment? And to figure out if it's an assignment, we would look to words of conveyance to assign title. And that's a matter of federal law under §261....*[A]*gain we don't have to use any special language, there's no notarisation requirement, but we would have to see language of conveyance, those special terms have to be used. But there would have to be language indicating transfer of title, as compared to a licence or security interest or something else. And again that's a matter of federal law.*"

499. Having tried but failed, through the invocation of *Schwendimann*, to persuade Prof. Thomas to subscribe to the more limited view of §261 for which BMS canvassed, counsel for BMS next invoked *Hewett v. Samonsite,* suggesting that it involved the Court of Appeals of Colorado holding that specific assignments of specific named patents were not valid under Colorado law, because they lacked consideration under Colorado law. Responding, Prof. Thomas held firm to his point, answering as follows:

> "[O]*nce again you have to have an instrument in writing, and then we have to look for a covenant with a conveyance. At that point then you would go to state law to interpret the contract and also to determine if there is agreement between parties that the courts would enforce, which would involve consideration. So, I agree with that. But, ultimately, you do have to look for that language of conveyance to see if there's an assignment. At that point, again, you go into state law.*"

500. Reference was also later made by counsel to *MyMail Limited* and *Leland Stanford Jr University v Roche Molecular Systems, Inc*. At no point, however, did Prof. Thomas yield any ground in terms of his interpretation of §261 or indeed as to the proper demarcation of federal and state law (his view in the latter regard being that "*a federal Court would apply state law when that's the governing body of law*").

ii. Acquiring an Interest in a Patent other than by Assignment

501. To the proposition that if a person acquires an interest in a patent other than by assignment §261 has no application, Prof. Thomas responded that "[t]*he only other way to transfer title of a patent, other than by assignment, that the Federal Circuit has recognised is by operation of law*

[federal or state]. *So, in those cases, §261 would not apply, although...ultimately you are going to see a writing in those situations.*"

502. To the suggestion that the decision in *Akazawa v Link New Technology International Inc.* offers support for the proposition that §261 applies where you have an assignment, but not otherwise, Prof Thomas responded:

> "*I'm okay with that assertion to the extent 'but not otherwise' means operation of law. This opinion plainly states there's two ways to go about transferring title; one of them is assignment, in keeping with §261, another is by operation of law, which I don't think I have to repeat, it's something that happens automatically without the intervention of any party....So if you look at* [the] *last paragraph it says the Court concludes* [the patent]*...was transferred...upon the death of the inventor....*[T]*hat would work, because that's operation of law. The other one says, however, if title didn't descend directly to the heirs but rather to the executor of the estate, then there must be a written assignment between that executor and the heirs. So, I think that paragraph spells out quite clearly that to have an assignment, it has to be in writing, or operation of law, full stop. There's no other way about it.*"

503. Counsel then turned to the *Enovsys* case. There, the question was whether the ex-wife of the inventor had a co-ownership interest in the patent. (The question arose because they had been married in California and California applied community of property rules.) Counsel drew Prof. Thomas's attention to the following observation of the court:

> "*It may seem strange at first blush that the question of whether a patent is valid and infringed ordinarily is one for federal courts, while the question of who owns the patent rights and on what terms typically is a question exclusively for state courts. Yet that long has been the law. Accordingly, we look to California law to determine who had an ownership interest in the patents after Fomukong and Whitfield's divorce in 2002"*,

then suggested that there was nothing in the foregoing which states that the only part of California law that would apply to the question of ownership is whether we can term it operation of law or an assignment. To this, Prof Thomas answered as follows:

> "[T]*his is an operation of law case. When the parties divorce, under California law the parties to the marriage may designate property that is not community property – for example, property that was pre-owned prior to entering into the institution of marriage – but everything else is essentially deemed community property that would be split between the divorced couple, evenly, under California law....So typically, that means some property is moving from one spouse to the other. And that happens automatically upon the divorce. So, that's operation of law. Again, I caution that US courts, when they write judicial opinions, are not writing treatises. They don't intend to - and in fact prefer not to - make broad statements about how the entire world is going to work. They're resolving the case in front of them. So, I think it's important to look at what the Court does say rather than what it doesn't.*"

iii. Section 261 has no bearing on equitable interests in property

504. Next, counsel for BMS posited that §261 does not have any bearing on equitable interests in property, to which Prof. Thomas responded as follows:

> "*I think the question on the table is §261 doesn't deal with equitable interests and property....It's true that if I say to you 'I promise to assign you, in the future, a patent'...that's an executory promise vis-à-vis 'I sell you the patent today' –*

and...cases like Dalzell *say that an oral promise to assign a patent in the future does not need to be committed to writing....*[I]*t's important to note, again, that the case law makes clear that this equitable interest arises only within that contractual setting, it's not otherwise been recognised by the US courts....In my professional opinion, a statement regarding an oral agreement between a former employee to assign rights in an invention to her employer* [the facts at play in *Dalzell*] *represents a far different candidate for equitable intervention than does the case of a corporate subsidiary. I don't believe...*Dalzell *speaks to the matter at hand....Section 261 does not apply to oral agreements to assign between employees and employers. That's the holding of Dalzell. I'm unable to go any further with this opinion*".

iv. Closing Remarks on Counsel's Propositions

505. It would be fair to state that counsel for BMS made no headway in terms of persuading Prof. Thomas as to the correctness of any of the propositions that she advanced concerning §261. In the exchange that follows counsel did a final 'run through' of her various propositions, eliciting some final observations from Prof. Thomas in the process:

"Counsel: *So, just to wrap this up, they were the propositions. And I don't think you've agreed with any of them. The first...was that §261 imposes a requirement of writing but it does not otherwise control the effectiveness of the assignment. You've restricted state law to sort of interpretation issues and things that are less than the full control of the effectiveness of the assignment, I think?*

Prof. Thomas: *I believe that* [issues such as]*...was the performance under the contract? was there consideration? ...did the parties exchange consideration? course of dealing in interpreting the contract....Those sorts of things would be state law. But the rest is §261: instrument in writing and has to be an assignment.*

Counsel: *The second proposition that you didn't accept was that §261 does not apply to the acquisition of an interest in a patent in any way other than by assignment. And you restrict that to §261 only doesn't apply if the change of ownership comes by something...called 'operation of law'....*

Prof. Thomas: *I don't think the phrase 'operation of law' is that contested in the United States....But, yes, that's right... assign...via 261 or...operation of law.*

Counsel: *...Then the final proposition with which you did not agree was that §261 does not apply in respect of equitable interests in patents and you restrict the authority of Dalzell to contracts, is it only contracts with employees or contracts to assign generally?*

Prof. Thomas: *It would not be limited to employment contracts, although that's where most of the work comes. And I would refer the Court to the Beam Laser and Digitech opinions....which expressly state that equitable interests are restricted to the contractual setting.*"

3. Timing of Patent and Equitable Interest

506. Moving on, counsel for BMS put it to Prof. Thomas that in the case at hand "*which concerns whether BMS Co has an equitable interest in an existing patent, the line of federal law that talks about whether an assignment is an assignment or an agreement to assign a future right...just doesn't apply, because the patent was in existence at the time that...the equitable interest came into being?*" To this, Prof. Thomas answered as follows:

"*I agree that I don't think that body of law is pertinent here. But it's not because the*

patent was already in existence, it's just what language was used in the instrument of transfer between the inventors and BMS Pharma. The break in the chain here is between BMS Pharma and BMS Co, because there is no assignment or really anything other than their corporate relationship. That's the break in the chain. So, I agree with you it's not pertinent."

507. Pressing her point, counsel for BMS then mentioned the *Abraxis* case and suggested that it was authority for the proposition that future rights only come into play where a right has not yet come into existence, that they only arise in respect of inventions not yet made, whereas in the present case the patent was already in existence when BMS Co said that it had acquired the interest. To this proposition, Prof Thomas responded as follows:

"*I very strongly disagree with that proposition with a very high degree of professional certainty. Many of these cases involve employee inventors. So, when somebody is onboarded to a company, they're expected to make or they may make inventions in the future. So, when the invention is reduced to practice, then at that point there will be this springing interest that would assign the invention from the employee to the employer. But, as we've discussed before, contracts are not limited to employment contracts, although that's where they most frequently arise in this setting, it seems.*"

508. Pressing her point still further, counsel invoked the decision in *Schwendimann v. Arkwright Advanced Coating*, pointing Prof. Thomas to the observation of Wallach J. that "*We have not held that such an exception should be extended to agreements assigning existing patents, especially where those assignments occur outside of the employment context*", and suggesting by reference to same that "*the question is whether the patent is existing or the application, right?*". To this, Prof. Thomas responded as follows:

"[L]*ooking at that paragraph, the first sentence, the one that begins with the word 'Finally'...I agree that when you have the interpretation of a contract, that is going to be generally a matter of state law. So, I'm fine with that....*[T]*hen there's a class of agreements which assign rights to future inventions. So, again this is when there's an employed inventor – you know, a scientist...work*[ing] *for a pharmaceutical company; her contract with her employer might say...'I agree to assign any inventions I develop in the future.' And once those inventions were made, the employer would enjoy an equitable interest and the employee would hold the legal title, under the wording of that agreement....What the Court says here in Schwendimann is that although we have an exception for federal law...we're not doing that outside the employment context....I'm not sure* [about] *the relevance of this language to this dispute, because we're not disputing the precise words of conveyance used in the covenants here.* [Here]*...there is no covenant, because there's no assignment between BMS Pharma and BMS at all. So, I'm just not sure how that's relevant*".

509. Counsel suggested the relevance to be that (i) federal law applies where the question is whether there's been an assignment of a future right, and (ii) federal law does not apply here because the right in question here was not a future right. To this, Prof. Thomas responded as follows:

"*I very strongly disagree with that proposition....Again, this is a fairly narrow issue. This is when you have a contract, an actual assignment, a written assignment between two parties and there's a language of conveyance and one says 'I hereby and do assign today', or 'I shall assign and will assign in the future'. Again, I agree that, generally, interpretation of contracts is a matter of state law. The Federal Circuit has said in this one situation we will federalise it so that we can have consistency about the language of conveyance. But then Schwendimann walks that back a little bit and says, well, that's only for future interests, it's not existing patents. This is a narrow holding regarding the choice of law for a particular covenant of conveyance. And that's it.*

There's no broader lesson to be taken here."

4. Equitable Interests and Group Companies

510. Counsel led Prof. Thomas to the segment of his report where he states that "*In the absence of a written assignment, US courts have refused to allow companies related to the patent owner to claim either a legal or equitable interest in that patent because the companies are commonly owned.*" Asked if he held to that position, Prof. Thomas indicated that he did. Counsel then asked if the decision of the Supreme Court in *Dalzell v. Dueber Watch-Case Mfg. Co.* did not fundamentally undermine the position that Prof. Thomas was adopting, at which point the following exchange occurred:

Counsel:	[Y]*ou say...that what's required by the courts is a written assignment before an equitable interest will be recognised. Do you stick by that position?*
Prof. Thomas:	*Absolutely.*
Counsel:	*Is that not fundamentally undermined by...Dalzell?*
Prof. Thomas:	*No, because...Dalzell... – though one sentence from...Dalzell case says that an oral agreement between parties may be enforced in equity – ...has no bearing upon the statement I made in this opinion.*
Counsel:	*But...you say that a written assignment is required....*[and] *Dalzell says an oral agreement is enforceable.*
Prof Thomas:	*The question is when will equity intervene? ...*[E]*quity will intervene when an employee uses his employer's facilities, is paid to produce an invention, is directed to produce that invention and then, despite the meeting of the minds that this invention will apply to the employer, heads off and gets his own patent, or sells it to another company....*[E]*quity will intervene in that. Equity will not intervene, the courts have consistently said, when a company chooses to incorporate a subsidiary, because there's nothing unfair or inequitable about a company forming a subsidiary. Because really the whole point of having a subsidiary is to isolate assets, not share them.*
Counsel:	*I don't think the courts have said that a written assignment is necessary before you can have an equitable interest between group companies.*
Prof. Thomas:	*I'm recalling* Abraxis *and* Spine Solutions*. This is a bit of a memory test, but I believe that statement is made in both Abraxis and Spine Solutions."*

511. Before moving on to a consideration of *Abraxis* and *Spine Solutions*, counsel for BMS suggested (again) "*that ownership of patents generally is for state courts*", to which Prof. Thomas again responded "*that when it comes to the conjunctive interpretation of contracts and ownership, that would be a matter of state law once the requirements of §261 are met*".

512. Counsel also queried whether the ability of BMS Co, as the parent of BMS Pharma, to call for the transfer of BMS Pharma's patent ownership was not the very definition of an equitable interest. Prof. Thomas did not agree, observing as follows:

> "*I do not believe there's any case in this bundle* [the bundle of cases before the court] *that uses the phrase 'right to call' and equates that with an equitable interest. It's true that an equitable title holder – in a sense the only thing an equitable title holder gets – is the ability to compel transfer of legal title. But...the Federal Circuit has never recognised that in the case of group companies.... I think it's important to recognise*

> *what we're talking about here is the standing of an enterprise to pursue a patent application. Standing is an important doctrine in the United States and I suspect elsewhere, because when an invention is made, a patent application is filed, a patent is procured, the effect of that act redounds to many actors in the marketplace....*[W]*hen we talk about group companies, the courts have stated, quite clearly, and consistently over many opinions that one doesn't own an equitable title, even though there is 100% ownership and not through some complicated diagram, you know, partial diagram of a massive multinational firm - I'm talking cases of very simple parent/subsidiary...*[where] *there's 100% ownership. Still they've* [*i.e.* the courts have] *denied an equitable interest.*"

513. To this counsel responded that she was not speaking about standing to sue (under §261) or standing to file (under §118), both of which were "*federal statute issues*". What she was talking about was equitable ownership of the patent "[a]nd *if I had the equitable ownership of a patent that you held the legal title in and I wanted, say, to make a filing or I wanted to sue, I would be empowered to require you to assign it to me and then I would have standing to sue, then I'd have standing to make the application. But what's at issue in this case is the equitable ownership.*" Professor Thomas disagreed with this, observing:

> "*What's at issue in this case is what does the term 'successor in title' mean in Article 4A(1) of the Paris Convention? And the choice of law here is US law. That's federal law. So, it's federal law about what is recognised as equitable title and who has standing to file a patent application in keeping with the Federal Patent Act.*"

5. *Spine Solutions*, *etc*.
(*Spine Solutions Inc* v. *Medtronic Sofamor Danek USA Inc* 620 F.3d 1305 (Fed. Cir. 2010))

514. In the course of introducing her questions regarding *Spine Solutions* counsel for BMS observed that her reading of case-law was that although §281 requires a patentee to sue (and that to be a patentee one had to be the legal owner) the courts will allow, somebody who has equitable title, standing to sue for equitable relief. To this proposition, Prof. Thomas responded as follows:

> "[T]*he case that refers to this is Arachnid Industries* [*Arachnid, Inc. v. Merit Indus., Inc.*, 939 F.2d 1574, 1578–80 & n3. (Fed. Cir. 1991)] *and it refers to a case, a District Court case called Apiezon....*[A]*s far as I know Arachnid and Apiezon are the only cases that speak to this. Arachnid is an early decision of the Federal Circuit, Apiezon is a District Court decision. What those cases say is that the equitable title owner may bring an action to declare that it is the legal owner of the patent – so this is the compel ownership part – and then may sue the recently dispossessed...title owner for infringement in just one action. So, normally you'd have to* [be]*...the legal title owner to bring the suit. These cases would allow the equitable title owner first to establish its legal title and then, at that point, sue for infringement the former legal title holder....*[T]*hat's how I understand Arachnid and Apiezon.*"

515. Counsel then turned to *Spine Solutions.* One of the reliefs sought in that case was damages, which are a remedy at law (not in equity). However, in that case it was the parent and parallel companies that were the trading companies and hence the entities that had sustained damage. That was why Spine Solutions wanted to have them in the proceedings. (To this Prof. Thomas indicated his agreement, stating that "[I]*t's very important under US law that the appropriate party be identified because, amongst other things, damages are based on the profits that the patent proprietor would have made absent the infringement. So, it's important to know exactly who is the patent proprietor*." He disagreed, however, with counsel's suggestion that the case "*isn't really that relevant, or potentially not relevant at all to the question of equitable ownership*", suggesting that the case is authority for the proposition that an understanding as between group companies is not sufficient to give ownership of some sort or, to quote Prof. Thomas' testimony on this point:

"[A]*n understanding between companies doesn't convey any cognisable interest that a court would recognise in the United States....The Federal Circuit considers whether an understanding amongst group companies conveys some sort of interest that would allow recovery and concludes that it would not....I think the Court's statement is clear, especially if you look to the left column on page 293, suggesting...how can any related company somehow possess any sort of interest? And...the interest being discussed here falls quite short of ownership. The interest argued...is an exclusive licence. That's...far short of ownership. Here, the Federal Circuit says you don't even qualify as a licensee, not to mention an owner. So, I think this precedent is quite powerful in favour of my arguments.*"

516. When counsel put it to Prof. Thomas that there was no statement in the judgment that an assignment would be necessary to show ownership, Prof. Thomas responded as follows:

"*The Court...says we're not even coming to an assignment, we're considering a licence which is far south of an assignment. It still says there's not even a licence. So that's, to me, pretty potent evidence of...what the Court would do next time....*[H]*ere they're saying the group company is not even a licensee. That, to me, is pretty powerful evidence that it wouldn't be considered an owner either.*"

517. In other words, Prof. Thomas relied on *Spine Solutions* as authority for the proposition that an understanding amongst group companies does not even convey a licence, not to mention ownership. When counsel put it to Prof. Thomas that what was decided in *Spine Solutions* was that the parallel company had no control over the intellectual property and that is what excluded the parallel company from standing (and the ownership required for standing), the following exchange occurred:

Prof. Thomas:	*Well, it's my understanding of the case that the fundamental fact that's being asserted here, that there's a chain of companies that have common ownership....*[a]*nd the Court insists upon a writing, even for a licence.*
Counsel:	*But the Court doesn't say you need a writing, the Court doesn't say you need an assignment.*
Prof. Thomas:	*On the right column on page 292 the Court does note that there is no oral or written agreement. And that is dispositive.*
Counsel:	*...Oral or written? You said that we need a written assignment.*
Prof. Thomas:	*Well, as we've gone through at great length, the Dalzell case does allow an oral agreement to assign....*
Counsel:	*But, Professor, when we were discussing Dalzell, you said that it only applied to...assignments from inventors. I asked you specifically whether it was not authority that an oral agreement to assign was enforceable in equity and you said it's only restricted to employee inventors.*
Prof. Thomas:	*So, I said the facts of the case involved an oral agreement between the employed inventor and his employer - again, someone who had been hired to invent, provided facilities, there was a meeting of the minds that the rights to the invention would inhere to the employer. So, I was speaking to the facts of the case.*
	[A review of the evidence shows that Prof. Thomas actually went somewhat further in this regard. I have already quoted previously in the main text above his observation that:

> "*I don't believe...Dalzell speaks to the matter at hand....Section 261 does not apply to oral agreements to assign between employees and employers. That's the holding of Dalzell. I'm unable to go any further with this opinion*".]
>
> *....[I]f counsel's suggesting that Dalzell has nothing to do with group companies, I agree with her.*
>
> Counsel: *I'm not suggesting that. I'm suggesting the opposite....It is you who said that Dalzell has nothing to do with group companies....*
>
> Prof. Thomas: *I don't really have any particular problem with evidence of an oral agreement between two parties, no matter who they are, to assign rights in the future. And that can convey an equitable interest. I'm not aware of any oral agreement that's been asserted in this case. And I would note in Dalzell the standards are quite high to show that.*

518. How is one to reconcile this last assertion with Prof. Thomas's previous point that "*I don't believe...Dalzell speaks to the matter at hand....Section 261 does not apply to oral agreements to assign between employees and employers. That's the holding of Dalzell*". I believe what Prof. Thomas means is this: (1) the holding of *Dalzell* is that 261 does not apply to oral agreements to assign between employees and employers; (2) while that is the holding of *Dalzell*, Prof. Thomas has "[no] *particular problem with evidence of an oral agreement between two parties, no matter who they are, to assign rights in the future. And that can convey an equitable interest*". (My one uncertainty in this regard is whether he means that he himself has no conceptual difficulty in this regard or whether he considers no conceptual difficulty to present under US law, though any uncertainty as to precisely what he means has no real consequence given his third and fourth points); (3) none of this assists BMS because "*I'm not aware of any oral agreement that's been asserted in this case*"; and (4) even if this was asserted (and I, like Prof. Thomas, am not aware of any oral agreement that has been asserted in this case) *Dalzell* sets "*quite high*" standards to showing same.

519. Counsel turned next to *Dickman* v. *Volmer*, a decision of the Wisconsin Court of Appeals which counsel suggested pointed to that court not considering that there was anything in federal law preventing it from having regard to understandings between group companies in terms of bringing equitable rights into being. To this, Prof. Thomas responded as follows:

> "[I]*f you look at the paragraph...that begins with the headnote numbers [6], [7] and [8], you'll see that there's a reference to* Dalzell*. And of course,* [when it comes to] Dalzell*, we're looking at one sentence...that talks about an oral agreement. Then there's the discussion of a different concept, which is noted by the Teets case. So, in...*Teets*...Judge Rader of the Federal Circuit recognised the 'work made for hire' doctrine...often known as the...'employed to invent' doctrine....Unlike many countries to which the US invites comparison, our Patent Act does not incorporate an express provision assigning rights between employees and employers. So, that is done as a matter of common law. And this is the 'implied in fact' contract....*[F]*or an American, an implied in fact contract would mean, for example, going to a restaurant and ordering a meal. I've actually never bargained with the server to say that I'm actually going to pay for it, but we all understand that that is how it's to be done. So, there's not a written agreement and there may not even be an oral agreement. The agreement is implied by the settings....[S]o that's* Teets*, and that's a distinct doctrine....It's not* [, however,] *my understanding of the facts presented* [in the case at hand] *that the break in the chain of title is between the inventors – the natural person who developed the invention – and BMS Pharma. The break in the title is between BMS Pharma and BMS Co. So I don't think the 'work made for hire' and 'employed to invent' doctrine is of any moment to this case.*"

6. *Abraxis*, *etc*.

520. Counsel turned next to *Abraxis*, another case of standing in which, this time, Abraxis was asserting that it had standing. It had obtained an assignment from AstraZeneca UK in June 2006. However, the patent had been owned by different companies in the AstraZeneca Group and, in effect, the Federal Circuit found that Abraxis UK did not have rights to assign in June 2006 and that Abraxis had commenced (or purported to commence) the proceedings before it had an assignment from AstraZeneca UK. At 1365-1366, the court held that the fact that AstraZeneca UK was in common ownership with the other AstraZeneca companies did not give AstraZeneca UK the right to assign. Then, at 1367, the court refers to the question of whether an equitable interest passed, with the court finding that (i) Abraxis improperly relied upon *Arachnid* to say that there was equitable title because there had been an agreement to assign rights in the future, (ii) that that improper reliance involved a misunderstanding of *Arachnid* (that it is not a future right if one just does not have the right at the moment), and (iii) that an equitable interest did not pass to Abraxis because AstraZeneca UK just did not have the right to assign.

521. Although Prof. Thomas in his answers to counsel concerning this case drew attention to the observation in *Abraxis* that "*Common corporate structure does not overcome the requirement that even between a parent and a subsidiary, an appropriate written assignment is necessary to transfer legal title from one to the other*" he did not seem especially to demur when counsel put it to him that the case does not reject any argument of equitable title arising between group companies as a result of their arrangement between them. At this point the following exchange occurred:

Prof. Thomas:	*Well, there is the sentence, "Without ownership, AZ-UK had no authority to convey either the patents' equitable or legal titles to Abraxis.*"
Counsel:	*I think there the Court is saying the assignment wasn't done in time and you can't give what you don't have. I think that's the extent of that.*
Prof. Thomas:	*There's also a discussion of* nunc pro tunc *agreements, but with the emphasis upon there needs to be an assignment. Yeah, it wasn't done in time, that's true.*

7. Section 118, *etc.*

522. Counsel moved next to suggest that in neither *Spine Solutions* nor *Abraxis* did the courts prescribe a requirement of any kind of assignment, let alone a written assignment, before an equitable interest can arise between group companies. After a few exchanges with counsel, Prof. Thomas observed:

> "*There is no authority that's been brought to the attention of this Court, or that I'm aware of, that recognises that any member of a corporate family holds an equitable interest in patent law for any purpose whatsoever. Doing so has a lot of problems, but on a doctrinal matter, one of the biggest is, of course, §118. Section 118 of the Patent Act confers standing to file a patent application. That was brought into the statute in the 1952 reforms. And if you read the legislative history and influential commentary of PJ Federico, who was a USPTO official at the time, prior to the 1952 Act, there was a strict requirement that the inventors, the natural persons, file a patent application.* [A problem arose]*...when you had an unavailable or uncooperative inventor, again, typically an employee, but not necessarily. So, §118 afforded the ability of, in the event of unavailable and uncooperative inventors, the ability of three parties to file a patent application on behalf of the inventor. The first was there's been a written obligation to assign; there's been a written assignment and the statute says or other proprietary interest in the matter. Which I think could fairly be called a*

beneficial interest. And under that statute, the assignee or the holder of the beneficial interest has the ability to file a patent application on behalf of the inventor and that would ultimately be obtained by the inventor. The very existence of that statute, as well as its amendment to allow assignee filing later in time, suggests that there is, or was, at relevant time, no broad ability for putative equitable titleholders to file patent applications. Congress strictly limited that. And, as I said previously, again, I really feel sorry for myself and everyone else who worked on the statute, because all of our amendments were unnecessary. It wasn't the case prior to the amendments in 2011 that an assignee could file directly, as in Europe. So, in Europe the company can file in its own name. For us, it's always the inventors. And there was a lot of discussion about the wisdom of having assignee filing; there was the sense that we should have the word of the individual inventor behind that application. So, we were talking about whether an assignee could file one, we weren't talking about someone who doesn't even have an assignment to file....That didn't cross our minds. And no one understood the statute at the time to allow someone who did not have a distinct chain of title from the inventor to the applicant to possess the ability properly to file that application. So, I respect Prof. Chisum [who takes, as will be seen later below, a different view]*,* [but] *I believe that he has misapprehended the significance of §118. I don't think he understands the significance of the amendment. I don't think he is as well apprised – again, I have a lot of respect for Prof. Chisum – I don't think he's as well apprised of USPTO procedures. I'll just say that I am a patent attorney and I've worked at the USPTO,* [and] *I consider myself fairly well apprised of USPTO procedures. The USPTO is very concerned about the right to act, and that is established through a chain of written assignments. That is the longstanding interpretation of that agency. And there's no reason to change it.*"

523. Counsel had of course been discussing the issue of equitable title only. Nonetheless, this digression on §118 and on the practices and expectations of the US Patent Office was of interest.

7. Corporate separateness; community property rules

524. Following on Prof. Thomas's examination-in-chief in which he made the point that ownership of a company does not deliver ownership of its assets, and that if it did, that would trespass upon corporate separateness, counsel made two points and sought Prof. Thomas's comments on same:

Counsel: *One point is that it is not BMS's case in this case that ownership of BMS Pharma automatically delivered ownership of the assets of BMS Pharma. What is argued in this case is that the particular legal and factual circumstances in the case meant that BMS Co could call for the assignment to it of the patent and it was, therefore, the equitable owner....I don't know if you want to comment on that?*

Prof. Thomas: *I understand your position.*

525. Counsel then returned to the decision in *Enovsys* and posited that case as an example of where, as between a married couple, two separate legal entities, there was a rule of state law that applied that meant that the property of one was co-owned by the other. Professor Thomas noted that (i) community property rules have evolved in the context of family law, (ii) he had not been called to give evidence on state laws concerning community property, and (iii) he is not a corporate attorney. A discussion ensued which included the following exchange:

Counsel: ...[I]*t will be Prof. Chisum's evidence, that the law of equity of the state has to be taken into account, in the same way as any community property principles or anything else, and...there is nothing excluding the taking into account of the law of*

equity...[I]*n fact, far from...excluding it, all of the authority of the Federal Circuit says that ownership of intellectual property is a matter of state law, full stop.*

Prof. Thomas: *Okay, let me offer a few observations....First, §118 does not afford a broad ability of entities to file solely on the basis of a beneficial interest. It's a very narrowly cabined statute. And that's the governing law. Patents are federal creatures, you get them through federal law, you enforce them in federal law, you transact them through federal law. So, the ability to file a patent application is not reflective of any sort of interest. And I think that makes good sense as a policy matter. Secondly, the quotations from the cases that are provided that say ownership's a matter of state law, that's because we're looking at interpretation of contracts. And I have no disagreement with the notion that once there is a written assignment then state law applies to interpret the contract....*[C]*ontracts can do a lot of things, but one thing is they can transfer ownership of a property right from one entity to another. So, I have no dispute with that fundamental proposition, but again, there's no broad invitation to have a broad introduction of state law. That's not the practice of the USPTO, for a very long period of time. That's not what Congress thought when it amended §118. And I believe a few isolated sentences are being divorced from their context and need to be understood within that context.*"

8. Six Further Cases

526. Counsel for BMS turned next to six further federal cases*, viz. Beam Laser Systems v Cox Communications Inc.*, *Steelcase Inc v Smart Technologies Inc.*, *DePuy Inc. v Zimmer Holdings Inc., Quantum Corp v Riverbed Tech*, *Top Victory Electronics v Hitachi Ltd*, and *Digitech v Newegg*.

i. General

527. Counsel put it to Prof. Thomas that only two of these cases post-date *Spine Solutions* and *Abraxis* so the other four could not be following them. Professor Thomas responded that "*that just demonstrates that this is a very longstanding principle*", adding that he did not know of any authority to the contrary and that the cases were all consistent in any event with *Spine Solution*s.

ii. Proprietary Interest and Group Ownership

528. Counsel posited that none of these cases pre-empted a finding under state law of equitable ownership "*arising out of arrangements in group companies*". To this, Prof, Thomas responded that "*as a common lawyer, I looked at what happened last time*" and that he "*looked at situations where a proprietary interest is asserted by a group company merely by dint of an understanding or just by ownership through some organisational chart....*[a]*nd they've been consistently rejected. So...the courts....*[have] *spoken in a resounding, consistent fashion.*"

iii. *De Puy*

529. Counsel drew Prof. Thomas's attention to the judgment in *De Puy* where Posner J. observes as follows:

"*The patent at issue in this case is owned by a wholly owned subsidiary of DePuy, Inc., the plaintiff. DePuy argues that since it owns the patentee, infringement of the patent hurts it because it is entitled to the patentee's profits. But by the same token*

someone who owned all the stock of a corporation could sue for redress of a tort committed not against him but against the corporation, and that is not permitted",

and posited that the only argument there was that De Puy was hurt by the infringement, not that it had an equitable interest. Prof. Thomas responded that Posner J., "*perhaps our greatest living judge*", decided in that case "*that members of the same corporate family don't possess proprietary rights of any sort in each other's acts....*[T]*he language on page 1238 in the left column describe[s] a beneficial interest that he rejects.*"

iv. *Quantum*

530. Counsel then turned to the *Quantum* and the observation by the court that the issue before it was "*whether, absent an alter ego...a parent company is automatically deemed to be the agent of its subsidiaries authorized to transfer patent rights*", positing that this meant that this was another case in which equitable title was not at play. To this, Prof. Thomas responded that at play was "*the question, which might ultimately be an obscure one...*[namely] *whether a principal and agent share...equitable title....But I think the point is that members of the corporate family don't share a relationship, even under an alternative theory of agency, which could be described as conveying a beneficial interest.*"

v. *Digitech*

531. Counsel turned next to *Digitech*, noting the observation, at para. 11, that "*Newegg does not allege that Acacia is the owner, assignee, or exclusive licensee of the 465 Patent,*" suggesting in this regard that "the difference between asking the Court to accept that you own the assets of a company only because you own the company and saying that you own the assets of a company because you could call for their assignment to you, [is]...a big difference". To this, Prof. Thomas drew my attention to the statement in the case that "'*The Federal Circuit has never held that a corporate parent has equitable title in a subsidiary's patents*'....[a]*nd citing cases. That's quite a strong and direct statement.*" When counsel referred to the separate statement in that judgment that "*The Federal Circuit has...alluded to equitable title where the rights to a patent are being held in a trust*" and observed that this was "a statement of what has been recognised, not a statement of what can be recognised", Prof Thomas responded as follows:

"*I have no fundamental disagreement with that statement, but would assert that the Federal Circuit has been the* de facto *Supreme Court of patent law for the last 40 years. Standing is a predicate issue in every patent assertion case. Under no circumstances, after all this time, has the Federal Circuit ever acknowledged an equitable or beneficial interest by dint of a corporate relationship. And given that it is a fundamental proposition of the United States that corporate entities are separate entities, I would be astonished to hear a contrary ruling and believe that that would incorrectly reflect US law and would be overturned by a competent authority.*"

532. Counsel also drew Prof. Thomas's attention to the fact that footnote 3 in *Digitech*..."*makes a very big statement that the Federal Court circuit has alluded to equitable title in the area of trusts.*" It was not clear to me what the significance of this was to the case at hand which is not concerned with a trust.

vi. Equitable Ownership and Group Ownership

533. Counsel returned to Prof. Thomas's observation that "*The Federal Circuit has never recognized an equitable ownership arising out of corporate ownership"* and observed that "*We* [BMS] *are not saying that there is equitable title here because of corporate ownership, we are saying there is equitable title here because BMS Co had the right to call for the assignment of the patent to it*", adding that "*if you're saying now, Professor, that the only proposition that you're*

advancing is that a parent does not have...ownership of the property of its subsidiary, then there might not be such a big difference between us." To this, Prof. Thomas responded that "*I'm having trouble finding a sharp distinction between the two propositions that you've raised.*" (And in truth it is difficult to see a fundamental difference between equitable title arising from corporate ownership and equitable title arising from control arising from that corporate ownership.)

vii. *Hologic*

534. Counsel posited that it is not correct to state that the Federal Circuit has never recognised an equitable title between a parent and a subsidiary: "Hologic *is the case that stands for that*". To this Prof. Thomas responded that "*The* Hologic *case...cites a number of federal cases and ends up piercing the corporate veil. So, it goes on this alter ego, if you read that; these corporations are in fact the same entity. I believe that that argument's not being presented in this case*".

viii. Pre-Litigation Assignments

535. Counsel posited that the reason few cases come before the Federal Circuit in which "*a group company is coming to sue and the parent says, 'Oh, I want to be in too, because I'm the equitable owner'*" is "*because in most cases, the parent company who is the equitable owner, will secure the assignment, or whatever needs to happen, before they sue. It's a very simple process, isn't that right?*" To this, Prof. Thomas observed as follows:

> "*I entirely agree that securing a written assignment between members of a corporate family is the accepted professional practice, it is what must be done to transfer title. So, I agree, cases like this where that hasn't been done and yet there's still an argument that there's a proprietary interest are...rare.*"

536. When counsel then put it to Prof. Thomas that BMS was being challenged here as to the validity of its patent and that if the situation was reversed and "*If someone* [here BMS] *was going to sue, the assignment would be made before suit*", Prof Thomas responded, "*I, again, agree that the professional broadly accepted standard is to execute a written assignment before*."

ix. Right of Public to Know Owner of Patent

537. Prof Thomas also touched in his last-mentioned answer on the proposition that the members of the public have a right to know who owns a patent, an observation which led to the following exchange:

Counsel:...	*Whether the public has a right to know who owns a patent doesn't mean that there isn't a world of ownership interest underlying that, isn't that right, Professor?*
Prof. Thomas:	*I'm not sure what you mean by a world of ownership interests. What does that mean?*
Counsel:	*It means that the name on the register does not always reflect who is the equitable owner.*
Prof. Thomas:	*Yet the public can consult the available record of the patent at such time as it issues and that would include the claim to the priority right and a record of the chain of title from the inventor. That's available when priority is claimed and every US prosecution history that is publicly available.*

x. *Ager*
(*Ager* v. *Murray* 105 U.S. 126 (1881))

538. Counsel noted that in response to Prof. Chisum's assertion that there is no federal case rejecting state law on ownership, Prof. Thomas had posited that *Ager* is just such a case. Counsel disputed that *Ager* was good authority to this effect and the following exchange occurred:

Counsel: *I have to put it to you that that is not a case where a federal court rejected state law on ownership....At page 9* [of the Book of Authorities, p.127 of the judgment it states]*...under 'Opinion'...'This is a bill in equity by a judgment creditor to subject to the payment of his debt the interest of his debtor in patent-rights...'....Now, if you look at the next paragraph, you can see there was absolutely no question about ownership. It was very clear who was the owner....Mr Ager was the owner, he then assigned to somebody else and it was then assigned back to him. So there's no question of ownership there, is there?*

Prof. Thomas: *There is, because if you go to page 11 and look at the left column, which cites from Justice Curtis...who was very active in the patent system and actually wrote on the topic as a commentator. And you can see he says: 'There would certainly be great difficulty in assenting to the proposition that patent and copyrights, held under the laws of the United States, are subject to seizure and sale on execution.' By state law. So, here he is saying that the federal law trumps the States. And of course, in my professional opinion, seizure and sale relate to ownership.*

Counsel: *I have to...disagree. He is not saying that the federal court trumps the State on ownership. The explanation of what he's saying...*[appears later] *down...where the court says....referring back to Mr. Justice Curtis:*

> '*The difficulties of which the learned justice here speaks are of seizing and selling a patent or copyright upon an execution at law, which is ordinarily levied only upon property, or the rents and profits of property, that has itself a visible and tangible existence within the jurisdiction of the court and the precinct of the officer; and do not attend decrees of a court of equity, which are in personam, and may be enforced in all cases where the person is within its jurisdiction.*'

The only point being made there is that the processes on execution of judgment debts relied upon being able to seize physical property and that when there was a patent at issue, there had to be a different mechanism at equity to say that...the debtor assigned the patent or that an agent would be put in place to assign the patent. So...I cannot see how this is a federal court overruling a state court on the issue of ownership.

Prof Thomas: *It stresses the paramount nature of the written assignment requirement, which is set out in §261. And, of course, I briefly state again the Federal Patent Act has a race notice system when the patent is sold to multiple actors. state law to the contrary would be pre-empted and, of course, state statute*[s] *of frauds would be*

prevented. So, in fact federal law blocks state law to the contrary all the time."

D. Re-Examination

539. The re-examination of Prof. Thomas was relatively brief. Counsel raised the issues and received the answers described hereafter.

1. Case-Law Considered

i. *Erie*

540. In response to questions from counsel for Teva, Prof. Thomas indicated that (a) it concerned the liability of a railroad company for an injury caused by negligent operation of a train, (b) it was, therefore, a plain tort case, (c) it had nothing to do with the subject matter of this case, (d) the issue arose in *Erie* as to whether, in determining liability, Pennsylvania state law applied or a federal general common law, (e) the Supreme Court had occasion to re-visit the case of *Swift* v. *Tyson*, which had previously held that in such cases where there was a diversity of states involved, one applied the federal general common law, (f) in Brandeis J.'s judgment, he (I) analyses *Swift v.Tyson*, (II) deals with the injustice and confusion caused by it, (III) addresses the fallacy underlying the rule declared in *Swift* v. *Tyson*, and (IV) indicated that the matter had to be remanded and determined in accordance with Pennsylvania law.

541. The following exchange also arose between counsel and Prof. Thomas concerning *Erie*:

Counsel:	*My friend referred you to the passage which is on p.70 and the proposition that where there is no congressional legislation or nothing in the Constitution engaging the federal jurisdiction, there is no justification for applying federal law, is that correct?*
Prof. Thomas	*....Yes, that's correct. The key language that I'd like to draw the Court's attention to, if I may, is the first phrase of the first paragraph on p.78, "Except in matters governed by the Federal Constitution or by Acts of Congress...". Here, the patent system is part of the US Constitution and is also part of federal legislation.*
Counsel:	*In your view, has the decision any relevance to what this Court has to decide with regard to the application of federal and/or state law?*
Prof. Thomas:	*None whatsoever.*

ii. *In re CFLC*

542. Counsel brought Prof. Thomas next to the decision in *In re CFLC Inc*, a case concerning the application of federal law to patent licences. The essence of Prof. Thomas's testimony at this point was captured in his observation that "[T]*his case has to deal with the relationship of federal and state law with respect to the assignability of patent licences. And here the Court identifies a paramount federal interest with respect to the topic of assignments*". When counsel put it to Prof. Thomas that the court reached this conclusion "*even though the federal law didn't specifically deal with licensing*", Prof. Thomas indicated that this was so and that "[A] *federal statute doesn't have to have an express provision. Courts will look to the policies involved to see if a State rule would conflict with a federal patent policy.*"

iii. *Digitech*

543. Counsel for Teva brought Prof. Thomas next to the *Digitech* case and, in particular, the following observation:

"*Patent rights are not acquired unless authorized by, and acquired in, the manner prescribed by statute. While courts permit true equitable-title holders to proceed out of fairness, equitable rules were not intended to circumvent policies and rules having their source in the patent statutes*",

and asked him what the relevance of this was to Prof. Thomas's evidence with regard to the application of federal law. To this, Prof. Thomas responded as follows:

"[E]*quity confines itself to situations where they're conscious the Court should intervene but conscious the Court doesn't intervene in a way that would expressly overturn what the Congress of the United States has enacted....So we're looking at a relatively limited framework for equity, especially when we're talking about ownership of corporate stock in which there's nothing inherently unfair.*"

544. Counsel also referred Prof. Thomas to footnote 3 (at p.5 of the judgment in *Digitech*) and asked Prof. Thomas what the relevance of the footnote was in terms of the *Digitech* decision. To this, Prof. Thomas responded as follows:

"*Footnote 3...is one of two sources, and I could cite other sources if you like that say the same thing. The only time the courts have recognised equitable title is in a contractual setting. It could be express, it could be implied – for example, on a work made for hire context. But there has to be some sort of contract where one party agrees to assign to the other explicitly. So, there's got to be some sort of transfer from one to the next. That's where equitable title comes in. It's not been expanded to other contexts....I'm not aware of any [contrary] authority and none has been cited in this matter.*"

iv. *Hewett*

545. Counsel brought Prof. Thomas to the decision in *Hewett*, recalled that Prof. Thomas had been questioned about the construction of an instrument which purports to be an assignment, referred Prof. Thomas to the following passage:

"*The patent applications, patents or any interest therein are assignable 'by an instrument in writing'. Patents and rights in patents are incorporeal personal property. An instrument which is claimed to be an assignment of a patent right but must adequately express an intention to transfer ownership of the patent right*",

and asked whether that passage is relevant to Prof. Thomas' evidence. To this, Prof. Thomas responded as follows:

"[A]*bsolutely. This is a state court opinion, it's not concerned with federal standing, it cites §261 for the proposition that...assignment of patents must be made in writing. And then it goes on to say there must be an adequate expression of the intention to transfer ownership. And observe the citation that is made next, United States v. Frasnov. And you can see by the F.Supp, the 'F' is federal. It's a policy of federal law to see there's – you know, how do we know it's an assignment? We have to see that there are words of conveyance. And that's what this Colorado case is referring to.*"

v. *Dalzell*, *Digitech*, and *Beam Laser*

546. Counsel queried of Prof. Thomas whether there is anything in *Dalzell* that is inconsistent with the propositions recited in *Digitech* and *Beam Laser*. To this, Prof. Thomas responded as follows:

"Dalzell...*is being cited for one single sentence in a disagreement between parties that has nothing to do with whether corporate subsidiaries or relatives own each other's patents. I don't have any fundamental disagreement at all with the sentence:*

> '*An oral agreement for the sale and assignment of the right to obtain a patent for an invention is not within the statute of frauds, nor within* [what is now §261 of the Patent Act]*, requiring assignments of patents to be in writing, and may be specifically enforced in equity, upon sufficient proof thereof.*'

...I'm not disputing that an oral agreement to assign in the future could be effective. The question is what...[*Dalzell*]*...which* [involves]*...a former employee against a former employer, has to do with this case. And I would note that...in* [*Dalzell*] *the* [equity] *argument didn't work. So, I just don't see the relevance to the matter in front of you.*"

2. Equity, Incorporation of Subsidiaries, and Calling for an Asset

547. Counsel for Teva noted that, under cross-examination, Prof. Thomas had indicated "*that there was nothing inequitable about a corporation forming a subsidiary and in the long history of US patent law, US courts have never held that a corporate subsidiary enjoys the sort of authority that has been asserted here.*" Counsel then asked of Prof. Thomas whether any of the cases to which he had been brought by counsel for BMS had led him to alter his opinion in this regard. Prof. Thomas answered in the negative. The following exchange then occurred:

Counsel:	*It was also put to you that the right to call for an asset was something that equated with an equitable interest. Would you care to comment on that?*
Prof. Thomas:	*The courts have not equated the so-called right to call with an equitable interest, not in a corporate setting.*

3. *Abraxis; Maquet*

548. Counsel for Teva drew the attention of Prof. Thomas to the paragraph in *Abraxis*, at 1366, where the US Court of Appeals, Federal Circuit, states that "*Common corporate structure does not overcome the requirement that even between a parent and a subsidiary an appropriate written assignment is necessary to transfer legal title from one to the other.*" Asked if he was aware of any case that contradicts or distinguishes this proposition, Prof. Thomas indicated that he was not.

549. Counsel then brought Prof. Thomas to the point in *Maquet* where the US District Court observes that "*The Court is wary of extending the doctrine of equitable title to situations where a corporate parent exercises control over a patentee subsidiary.*" Professor Thomas indicated that he believes that this accurately reflects U.S. law.

4. *Enovsys*

550. Counsel noted that *Enovsys* had been put forward as a case that supports the case advanced by BMS in these proceedings, "*but you offered the view to the court that this was a case which provided for a transfer of title by operation of law, is that correct?*" To this, Prof. Thomas responded as follows:

"*Yes. Patents can be transferred through assignment or through operation of law. So, state law is often the source of the operation of law....*[a]*s far as I can tell in...transfer of estates through intestacy and through dissolution of a marital estate. But I'd like again to stress that these happened sort of automatically. Often the party is being*

dispossessed of property he might prefer to retain. And there's an actual transfer. state law is saying there's a predecessor and the property's transferred to a successor. And those are the hallmarks of operation of law. And this case is consistent with that....[O]*nce the California court recognised the effect of the divorce...then you're looking to effect a judgment. That's what's going on in this decision*."

17

The Evidence of Professor Chisum

A. Introduction

551. Professor Donald Chisum is a former law professor at the University of Washington and Santa Clara universities and the author of a renowned treatise on U.S. patent law, *Chisum on Patents*.

552. Subject to para.4 of this judgment, an abridged version of Professor Chisum's written evidence is set out at Appendix 2. I respectfully invite readers of this judgment to read that appendix and then resume reading here. An account of the evidence that he gave when examined, cross-examined, and re-examined follows hereafter.

553. In his witness statement, Prof. Chisum states, amongst other matters, as follows (at §§7-8 and §10):

> "*I have been asked by McCann FitzGerald LLP, solicitors for the Respondent, Bristol-Myers Squibb Holdings Ireland Unlimited Company to act as an independent expert in these proceedings….I have been asked to provide opinions on issues of United States law that have arisen in regard to ownership and succession of title to a United States patent application and a right to claim priority based thereon as between companies incorporated in the State of Delaware….I have been asked in particular to comment on an Expert Statement of Professor John R. Thomas dated 14 April 2022*".

B. Examination

1. Federal Law and State Law

554. Counsel for BMS asked Prof. Chisum to outline how the two systems of law within the United States – federal and state law – relate to each other in general terms (not specifically on patents). Professor Chisum indicated as follows:

> "[T]*he United States...has a federal system of law in which, on the one hand, you have state courts and state law and you have federal Courts and federal law. If I had to use any sort of general description of the relationship, I would say state law is the general, whereas federal law is always just the specific. And the same applies to the Court system. So, if you take...a metaphor...if you thought of the whole body of jurisprudence as a big ocean, state law would occupy all the water, federal law would be particular islands....*[S]*o, federal law comes into play generally when there is just a statute or a federal constitutional provision at issue. And I can't emphasise enough that in terms of all the relationships you think about, transactions and occurrences, the overwhelming percentage of them are governed by state law....*[H]*aving said that...a very important federal item is the...patent system. But...state courts have general jurisdiction, which means they can entertain all kinds of cases. Hypothetically, just as an example, a Delaware pharmaceutical company could sue an Irish pharmaceutical company in the Delaware state courts....And there's an appellate court system* [*i.e.* within each state]...[and] *the ruling of those courts, including by their Supreme Court becomes the definitive interpretation of that state law. Now we have, on the other hand, the Federal Court system. Those courts you would not describe as having any general jurisdiction. They only have jurisdiction if there's a specific statutory grant. And the two major categories, the most important is cases that arise under federal law, such*

as patent law....[a]*nd then they also have jurisdiction, something called diversity and citizenship. So, in my hypothetical, in the US company, Delaware corporation, sued the Irish, the Irish company could 'remove it' to federal court. The idea may be the federal courts would be less favoured towards the Delaware...corporation....So...the state courts have general jurisdiction, but there is an exception, an important one, that certain areas are exclusively for the Federal Courts. And one of them is cases arising under patent law. But that's defined...pretty narrowly. That is a suit for infringement of a patent, for example. And the Patent Act defines...who has a remedy to sue. It has to be the patentee, which means somebody who has a legal title by assignment and that's tied into jurisdiction. So...there's a lot of discussion between Prof. Thomas and myself about standing; well, you shouldn't get the impression that standing is some kind of formal requirement, it's a very important part of the Federal Courts' jurisdiction. So the federal courts often realise that...they are limited and they have to keep their power within their defined jurisdiction or otherwise they are encroaching on the predominance of state law.*"

555. A couple of points might usefully be made following on the above quote. First, (and this is something that Prof. Thomas agrees with) when state law does apply, the federal courts have to apply state law, that is the *Erie* doctrine. (I should perhaps note in passing that the *Erie* doctrine, it seems to me *is* relevant to this case. This is because, as I understand Teva's submission it maintains that when federal courts make utterances about things generally, that has an impact on what Delaware law would do, but in fact, pursuant to *Erie*, the position is that when state law applies, the federal courts have to apply state law.) Second, as I describe later below, Prof. Chisum was also in his examination-in-chief brought to the question of pre-emption of state law. Thus, when asked about the pre-emption rule, he responded that there is no question but that federal law, when it applies is supreme, "[b]*ut there has to be a conflict....And in the ownership area, there isn't a conflict, for the most part.....There is no doubt that Federal law is supreme, Prof. Thomas is right. But I just don't see, there's just not a conflict here.*" Asked if there was no conflict because federal law just does not apply, Prof. Chisum indicated that this was so.

2. The Patents Act

556. Asked to summarise what generally is provided for in the Patents Act, Prof. Chisum indicated as follows:

"[T]*he patent statutes provide that an inventor can obtain a patent, first and foremost, you need to file a timely patent application fully disclosing the invention. Usually that has to be an inventor, a human being. We have recently started the debate whether artificial intelligence can be an inventor and at least the United States is saying no...this is about humans who make inventions. So, you file the application and then it will go through an examination process by the Patent and Trademark Office. And there might be appeals. You have to state your invention in claims. There might be amendments to the claims. And eventually, hopefully, if you're the inventor, you obtain issuance of patent. The Patent Act then provides that that becomes an item of personal property, which is assignable and it gives exclusive rights. And there's a very precise definition of what those rights are. It's right to exclude others from making, selling, using the invention, importing it and the like. And then it also [specifies]...remedies, an injunction and damages.*"

3. Ownership of property (including intellectual property) a matter of state law

557. Counsel for BMS put it to Prof. Chisum that ownership of property generally and of intellectual property, including patents, is a matter for state law, and asked Prof. Chisum if he could inform the court of his authority for that proposition. The following exchange then ensued:

Prof. Chisum: *There...is no federal law about, for example, the ownership of property and how it's transferred. And that has been our history for more than 200 years....*[E]*arly on it was established that the patents are property, but they become subject to the judicial process regarding ownership. Now, I think maybe to save time I'll hone in on the one specific issue that Prof. Thomas and I, to some extent, debate. There is this statute, Section 261, that talks about a patent application or a patent being assignable at law - a key phrase - by a written instrument. Now...that's a very old statute, almost the exact wording was enacted in 1836. Because the US had an early patent system....*[W]*hen that was first enacted, people started to argue 'oh, this changes that idea that patents are property in the state law', and in particular that it interfered with the traditional powers of the Courts of Equity...to enforce an obligation to transfer rights to an invention or to a patent. And that argument was made and rejected by a series of state courts that said 'no, this talks about, you know, an assignment, first of all, an assignment means a formal conveyance in writing and at law, and we're talking about equity'. I mean, it's a little more complicated than that. So they were saying, in effect, this statute does not interfere with the power of Courts of Equity, including state courts, applying state law to recognise, in effect, equitable title in inventions and patents. What's interesting is those were State Court decisions. But you come to, I think it's 1893 that, the Dalzell case, which I talk about in my report....*[a]*nd the Supreme Court, in a relatively short analysis, says 'that's right...an equitable enforcement, specific enforcement, even an oral one, is enforceable and nothing in this statute is contrary to that.'...*

Judge: *Professor Thomas tried to confine that to the employer/employee context....Is that right?*

Prof. Chisum: *I think that's wrong, for the following reason: one of the things the Supreme Court did is cite more cases....*[a]*nd after Prof. Thomas started questioning it, I scratched my head and said I'm going to go back, I want to make sure I'm not being unfair. And I looked at those cases and some of them indeed involve enforcing* [a contract]*....But they weren't all of that. One...involved a copyright, for example. But the statutory scheme was the same. And another involved, like, a contract in which they agreed to share one-third, one-third interest in the patents. And that was not an attempt to enforce, you know, the employer's right to employ, that was an oral contract to divide up the ownership and share the proceeds. So, I don't think it's really fair to say that Dalzell is limited simply to the employee. I can see why he would say that, because that is the facts of the Dalzell case, but I don't think it's been read that way ever since. It's been applied by State Courts as meaning that there are their equitable powers to enforce are not precluded by Section 261....*

Counsel: *...I believe in fact that Prof. Thomas' evidence slightly changed in the course of oral evidence in relation to Dalzell and...and I might mention that later...*".

4. The *Stanford* Case

558. Counsel for BMS turned next to the proposition in Prof. Thomas's report that the *Stanford* case has implications for the joint application of federal and state law to the question of ownership.

In his report, Prof. Thomas states, amongst other matters, as follows, under the heading "*Applicable Law – U.S. Federal or State Law*":

> "*28. There are two court systems in the United States: federal courts, which operate under the federal laws of the US, and state courts, which operate under the laws of each respective state. All cases arising under US patent laws must be heard in a federal court.*
>
> *29. Where applicable, the federal court will apply both state law and federal patent law where issues of state law are intertwined with federal patent law issues. For example, in* Tyco Healthcare Group LP *v.* Ethicon Endo-Surgery*, 587 F.3d 1375 (Fed. Cir. 2009), the Federal Circuit applied Delaware contract law to construe an assignment allegedly transferring ownership of the asserted patents to the plaintiff, Tyco Healthcare. The Federal Circuit ultimately concluded that Tyco Healthcare had not shown that it owned the patents that it had asserted and therefore dismissed the case for lack of standing.*
>
> *30. In the US, state law governs the ownership of property (including intellectual property) and the interpretation of contracts. Therefore, the question of who has legal title to a patent is a matter of state law (*Enovsys LLC *v.* Nextel Commc'ns*, Inc., 614 F.3d 1333, 1342 (Fed. Cir. 2010)).*
>
> *31. Notwithstanding the general applicability of state law to questions regarding ownership of property and the interpretation of contracts, federal law governs the way in which an assignment of patent rights (including the right to claim priority) can be made.*
>
> *32. The leading case in this area,* Board of Trustees of the Leland Stanford Junior University *v* Roche Molecular Systems*, Inc, 583 F.3d 832,841 (Fed. Cir. 2009), aff'd, 563 U.S. 776, 131 S. Ct. 2188, 180 L. Ed. 2d 1 (2011), summarized the situation as follows:*
>
> > *'[T]he question of who owns the patent rights and on what terms typically is a question exclusively for state courts ... However, this rule has exceptions; the question of whether contractual language effects a present assignment of patent rights, or an agreement to assign rights in the future, is resolved by Federal Circuit law.'*
>
> 33. *There is therefore an overlap between state law and federal law regarding the transfer of patent rights and the two must be considered together in order to determine whether a particular purported transfer of patent rights is valid*."

559. Professor Chisum offered the following interpretation of the *Stanford* case:

> "[O]*ne of the things, I don't think Prof. Thomas points out, the Supreme Court granted review of that case and addressed sort of another issue about ownership in which I would say they recognised that...there wasn't a federal statute establishing ownership....*[In that case there] *was a researcher at Stanford, I think he was under an obligation to convey, probably a contract, to convey his rights to Stanford, but he was allowed to go consulting with a private company and while at the private company, he signed an agreement....*[T]*he Stanford agreement was framed in terms of an agreement to assign in the future, whereas the one in the private company: you hereby presently convey, assign the future invention....*[S]*ubsequently...Stanford applied for the patent, got a legal assignment...and then sued the successor to the private company. And the private company said... 'no, we own this, ...because of that prior assignment....And because we own it, though you seem to have legal title, you don't, because we own it.' ...*[T]*he Federal Circuit, applying this previous exception they had...said... 'all right,*

federal law governs this one exceptional area, and that is in interpreting whether an agreement is one to presently assign a future interest or is one to assign it in the future when the invention actually arises'. And they said, you know, that the Stanford agreement was only a promise to assign in the future...and...the agreement with the private company [was]*...a private conveyance. So they obtained ownership. And that defeated Stanford's standing, even though they had legal, a chain of apparent legal title....But they are applying a distinction they applied before in DBB. They said...generally state law governs ownership, including ownership of title, but we, for a variety of reasons have adopted a specific exception, which is for these agreements, how to interpret an agreement. And it's kind of an odd area of law because they put so much weight on do you say 'I hereby grant' or 'I will grant'....But that is the Federal Circuit. That's what they say. But the whole point of creating an error exception is that it is an exception. It's one of though* [*sic* – 'those'?] *islands, if you will, in an ocean where generally state law controls.*"

5. Section 261 and Ownership

560. Counsel for BMS noted that Prof. Thomas had indicated in the course of his oral testimony that §261 applies to all transfers of ownership unless they can be characterised as transfers by operation of law. Counsel led Prof. Chisum to the portion of §261 which states that *"Applications for patent, patents or any interest therein shall be assignable in law by an instrument in writing*" and asked Prof. Chisum to identify the specific impacts of that provision. In reply, Prof. Chisum indicated as follows:

"[I]*t means that if you are assigning...in law, meaning you're assigning legal title, it's by an instrument in writing. So, it is dealing with assignments of legal title, assignments at law and not, for example, in equity....*[I]*t is...read to mean...at least in the standing cases, to mean if you're needing to rely on a chain of legal title, there is a writing requirement....*[I]*t's not really clear that this is the only way for legal title to be assigned. What is clear is that it doesn't, going all the way back to Dalzell and all that history, it doesn't affect equitable enforcement of obligations defined by state law, however defined by state law.*"

6. *Schwendimann*

561. Counsel for BMS led Prof. Chisum to the *Schwendimann* case and asked Prof. Chisum as to the legal purport of same. To this, Prof Chisum answered, "*I think it means pretty clearly what the court says, that...§261 imposes a written instrument requirement*". Invited to comment again on the link between §261 and ownership, the following exchange occurred at this juncture:

Counsel:	*Prof. Thomas...says that §261 applies to all questions of ownership unless change of ownership is done by what he characterised as operation of law....I wonder can you just touch on that again briefly?*
Prof. Chisum:	*I think it's pretty clear...in light of the history, in light of the language of 261...*[that it] *is dealing with transfers at law, meaning of legal title. And that 'at law' phrase has real meaning and...had even more meaning...in 1836 when it was enacted. At that time the US Courts were very much into...the English system of law and equity. And that's, of course, what the State Courts then said and then the Supreme Court affirmed....*
Counsel:	*Could you...comment on what, if any, impact §261 has where the interest is acquired other than by assignment?....Did...Section 261 apply?*
Prof. Chisum:	*No.*

Counsel *...So, just to gather that together, you've given evidence that §261 imposes a writing requirement for an assignment in law, and that's all. You've given evidence that substantive ownership is governed by state law, apart from that one exception relating to assignments of future rights. Taking those two points of your evidence together, can you comment on whether federal law applies to the question in this case, the question in this case being whether BMS Co had an equitable interest in an existing patent in 2001?*

Prof. Chisum: *I think that's a question to be decided under Delaware law according to the authorities, including the Delaware courts...*

7. The Federal Courts and Equitable Ownership

562. Counsel for BMS asked Prof. Chisum to comment on the propositions that the federal courts place constraints on when equitable ownership can be recognised. In response, Prof. Chisum observed as follows:

> "[I]*f an issue of state law arises in federal court, they do their best. But they are bound to follow state court authorities, if there are any. And, furthermore, whatever the federal court says is not binding...on the state courts....State court decisions are not appealable to the Federal Circuit or the District Courts. They are reviewable by certiorari, by the Supreme Court, but only on federal issues. So, what the State court says is final. Now, the State Courts, as I said, have the final word, whereas the Federal District Courts in standing cases, I think several of them that are cited there have discussed...general corporation principles. I'm not sure...it's clear that they were applying Delaware law....*[E]*ven if they were, that would be only...an opinion about Delaware law.*"

563. Asked if the foregoing relates in any way to the *Erie* doctrine, Prof. Chisum responded that previous to *Erie* a federal court would, in a diversity dispute, apply the general federal common law, only in diversity cases. And the Supreme Court, in 1938, in *Erie*, held that even in diversity cases a federal court enjoys jurisdiction but the applicable law is the law of the state and the state court decisions are binding.

564. Asked also in this regard about the pre-emption rule, Prof. Chisum responded that there is no question but that federal law, when it applies is supreme, "[b]*ut there has to be a conflict....And in the ownership area, there isn't a conflict, for the most part.....There is no doubt that Federal law is supreme, Prof. Thomas is right. But I just don't see, there's just not a conflict here.*" Asked if there was no conflict because federal law just does not apply, Prof. Chisum indicated that this was so.

565. It seems to me that the key point when it comes to *Schwendimann* is that the federal courts decide when federal law applies and when state law applies and in this regard the federal courts have decided in *Schwendimann* that in the case of ownership of property state law applies. So, in this case that means that the priority issue falls fundamentally to be decided by reference to Delaware law.

8. *Spine Solutions*

566. Asked for his reading of the *Spine Solutions* case, Prof, Chisum responded as follows:

> "*Okay. Let me take my stab at it....*[Y]*ou had the parent and you had the subsidiary. The parent has sued for infringement. The parent is title owner, nobody contends other way....No contention that...the subsidiary has equitable title, much less legal title. But they want to join the subsidiary in order to get better damages, because it's the subsidiary that's making and selling products, not the parent....So we're not talking*

about standing of the plaintiff to bring the suit....[N]*ow, there's a separate body of law we haven't talked about which says if you're an exclusive licensee under a patent, you can join the suit brought by the legal patent title owner. But you have to have an exclusive licence....So, in this instance...there just wasn't a basis for saying there was an exclusive licence. And there was no contention that there was equitable title or any basis for an equitable title under state law....And then they* [the court] *said... 'well, if we followed your argument we would have to find that there was...an exclusive licence and, therefore, standing on that ground, every time you had this kind of parent/subsidiary relationship, and so we won't do that'. But again...it wasn't a contention that they had...equitable title to the whole patent.*"

567. Asked to comment on Prof. Thomas's reliance on this case for the opinion that intercompany arrangements other than assignment are not sufficient to confer equitable interest, Prof. Chisum indicated that "[f]*ederal law doesn't have anything to say about that....And he may be right, if he were an expert on Delaware law, and maybe he is, but I didn't understand him to be opining on Delaware law.*" (This understanding was correct.)

9. *Abraxis*

568. Counsel for BMS turned next to the *Abraxis* case. There, *Abraxis* had received an assignment from one AstraZeneca company and its standing to sue on the basis of the patent assigned was opposed on the basis that the AstraZeneca company in question didn't have rights in the patent at the time of the assignment. Asked to comment on the case, Prof. Chisum observed as follows:

"[T]*hey're applying 261, which says if you have legal title, there has to be writing. The facts in Abraxis was there was a gap in the chain of legal title....The parent's problem is they hadn't obtained an assignment from a subsidiary that then owned legal title. So, since we're talking about legal title and standing to bring a suit, that was the problem that the court pointed out....And the fact that they were a parent and subsidiaries does not satisfy...*[the] *261...requirement that they'd legal title. That's, I think, undisputed.*"

569. Later the following exchange occurred:

Prof. Chisum:	[T]*he alternative assertion, by the plaintiff was going back to that agreement with the parent that the parent somehow or another conveyed equitable title.... Now, the problem with equitable title is it generally isn't sufficient for bringing a patent infringement suit....*[T]*here are cases that say, or suggest, that in some circumstances equitable title will be sufficient if you're seeking equitable relief. That gets a little complicated, but I don't think it's...necessary to understand what they're saying here. Because...*[here] *the equitable and legal title was in the subsidiary....*[A]*ll it* [is authority for, is that]*...if you really, really had equitable title there might have been an argument that you, in this case, had standing to sue, because this was not an action for damages....But...a key point here, as I said,* [is the virtual concession as to non-ownership of]*...either equitable or legal title....*[no laying of]*...a basis under state law for saying that...there was equitable title in the parent.*
Counsel:	*So, there was no argument to that effect that you can see here, Professor?*
Prof. Chisum:	*Exactly*.
Counsel:	...[C]*an you read those cases as saying that ownership of a company does not of itself automatically give ownership of a*

company's assets? ...

Prof. Chisum: *I think these cases clearly say if you have a parent/subsidiary corporation the co-ownership doesn't satisfy the requirement that there be an assignment of legal title for standing purposes. That's what they say....Ownership is a matter of state law....*

Counsel: ...[If] *these cases were authority for the proposition that ownership of a company did not of itself give you ownership of the company's assets, if that could be drawn from these cases – and I'm not asking you to say that it could be – but if it could be drawn from these cases, would that mean anything for the application of state law to the facts and circumstances of any particular case?*

Prof. Chisum: *No.*"

10. 35 U.S.C. §281
Remedy for infringement of patent

570. Professor Chisum was brought by counsel for BMS to §281 (which provides that "*A patentee shall have remedy by civil action for infringement of his patent*") and was questioned about same. The following exchange ensued:

Counsel: ...[C]*an you tell me what, on its face* [§281]*...requires, in order to have standing to sue?*

Prof Chisum: *It requires you to be a patentee....*

Counsel: *What do you need to be in order normally to be a patentee, Professor?*

Prof. Chisum: *You have to, essentially you have to have an assignment of legal title....There's a definition of patentee in §100.*

Counsel: *...Is standing to sue ever extended beyond the owner of a legal title? ...Is there ever standing in a person other than a legal title owner to sue?*

Prof. Chisum: *Generally not. There are some cases,* [the] *Federal Circuit in very limited circumstances has suggested that owner of equitable title could bring a suit. Frankly, that is disputed, because of the language of the statute.*

Counsel: *But it happens actually, Professor, doesn't it?*

Prof. Chisum: *Not often.*

Counsel (Teva): *She shouldn't lead her own witness...*"

11. 35 U.S.C. §118
'Standing to file'?

571. Section 118 provides, amongst other matters, that "*A person to whom the inventor has assigned or is under an obligation to assign the invention may make an application for patent*". Counsel for BMS brought Prof. Chisum to this provision and the following exchange then occurred:

Counsel: [C]*an you just tell the Court, perhaps, I know that Section 118 has been amended and the section that we're looking at here is not the section that applied in 2001, but could you just inform the Court of what the old section provided in terms of who has standing to file a patent application?*

Prof. Chisum: *...Prof. Thomas uses the phrase 'standing to file'. I have never used, or heard of using 'standing* [to file]*'. 'Standing' has a very definite powerful meaning in terms of bringing judicial actions. We don't usually talk about 'standing to file'. And...he started to talk*

about...standing to file [being*]...like standing to sue. And that was news to me. Now there are statutory provisions on who is authorise*[d] *today* [to] *file an application and...I think I first referred to §118 to confirm one important proposition, that there could be equitable ownership in an invention and, therefore, in the application for a patent...*[e]*ven if there had not been a written assignment. So, if you had an employee, the better procedure is always to get them to file a written assignment of title. But even if there hasn't been, the employer would have arguably...going...back to those old cases...equitable title. The important part of this statute is you can't argue that the patent statute steamrolls over any of those concepts of equitable...ownership....*

Counsel: *...In 2001 could the owner of legal title file for a patent if the inventor was available to file?*

Prof. Chisum: ...[T]*hey could file, but...in the name of the inventor.*

Counsel: ...[W]*ere there provisions in respect of the owner of legal title or equitable title to file if the inventor was not willing....or could not be found?*

Prof. Chisum: *Yes. 118....*

Counsel: *Was the owner of equitable title...in any different position to the owner of legal title in that respect, in terms of an ability to file if the inventor was not able to be found or refused to file? ...Did they also have an ability to file if the inventor wasn't available or refused?*

Prof. Chisum: ...[T]*here were some problems if you're dealing with an uncooperative inventor. Ultimately, sometimes lawsuits are brought, what the equitable title owner will have to do sometimes is sue the employee, saying; 'oh, you're being uncooperative'....So, in some circumstances the equitable title owner's remedy is to force an assignment by the inventor. But that is an available equitable remedy in state court. In state court....*[b]*ecause it's state law.*

12. *Digitech*

572. Counsel brought Prof. Chisum to Footnote 3 in the *Digitech* case. Footnote 3 states as follows:

"*The only Federal Circuit cases that recognize an equitable title to a patent involve contractual arrangements to assign rights in inventions between the asserted equitable title-holder and the inventor. E.g.* Film Tec*, 939 F.2d 1568;* Arachnid*, 939 F.2d 1574;* DDB Techs.*, 517 F.3d 1284. The Federal Circuit has also alluded to equitable title where the rights to a patent are being held in trust. E.g.,* Gellman *v.* Telular Corp.*, 449 F.App'x 941, 944 (Fed. Cir.2011).*"

[It is worth recalling at this juncture the exchange that took place between counsel for Teva with Prof. Thomas regarding the *Digitech* case. As I have recorded separately in this regard:

> "*Counsel for Teva brought Prof. Thomas next to the Digitech case and, in particular, the following observation:*
>
> > '*Patent rights are not acquired unless authorized by, and acquired in, the manner prescribed by statute. While courts permit true equitable-title holders to proceed out of fairness,*

> *equitable rules were not intended to circumvent policies and rules having their source in the patent statutes*',

and asked him what the relevance of this was to Prof. Thomas's evidence with regard to the application of federal law. To this, Prof. Thomas responded as follows:

> '[E]*quity confines itself to situations where they're conscious the Court should intervene but conscious the Court doesn't intervene in a way that would expressly overturn what the Congress of the United States has enacted....So we're looking at a relatively limited framework for equity, especially when we're talking about ownership of corporate stock in which there's nothing inherently unfair.*'

...Counsel also referred Prof. Thomas to footnote 3 (at p.5 of the judgment in *Digitech*) and asked Prof. Thomas what the relevance of the footnote was in terms of the *Digitech* decision. To this, Prof. Thomas responded as follows:

> '*Footnote 3...is one of two sources, and I could cite other sources if you like that say the same thing. The only time the courts have recognised equitable title is in a contractual setting. It could be express, it could be implied – for example, on a work made for hire context. But there has to be some sort of contract where one party agrees to assign to the other explicitly. So, there's got to be some sort of transfer from one to the next. That's where equitable title comes in. It's not been expanded to other contexts....I'm not aware of any* [contrary] *authority and none has been cited in this matter*'".

Counsel asked Prof. Chisum to comment on how Footnote 3 relates to the idea that the federal courts place constraints on state courts on the question of equitable ownership. To this, Prof. Chisum responded as follows:

> "*Prof. Thomas emphasises that you read language in cases in context. And I totally agree with him. So you need to read this in the context that this is a standing question. So, the issue would be: 'is equitable title enough to have standing to bring an infringement issue, even one seeking equitable relief?' There are substantial arguments to say no. So, what the Judge is saying in this Footnote 3, read in context, is 'look, the Federal Circuit has recognised this only, like, in one or two instances. So, it's not clear at all whether they would recognise equitable title.' And I think you really have to say implicitly recognise equitable title as providing sufficient standing. Now, you have to understand, again, I mentioned at the very beginning, the federal courts are very cautious about their jurisdiction and extending it beyond what they're into in a case. And if they are too loose in applying this...rule, they are impeding* [*sic* – 'impinging'?] *on traditional state law and state court matters. So, that's basically what I read that footnote as being; you know, a contractual arrangement to assign rights and inventions between an equitable title owner and the inventor. That's the only type of case they have recognised. So...this footnote is not saying that 'oh, the Federal Circuit would deny equitable title in any other situation, equitable title to the patent'. That would be extraordinary. I don't really think Prof. Thomas was suggesting that....there can never be equitable title in a patent in a corporate situation.*

Ever? Whatever facts there are and whatever state law said?"

13. *Hologic*

573. Counsel for BMS brought Prof. Chisum next to the *Hologic* decision and asked what the federal District Court was recognising in this case. To this, Prof. Chisum responded as follows:

> "[T]*he...District Court...is recognising that because of this corporation relationship plus complete control and the like, I think it's a parent/subsidiary...has equitable title,* [that it] *has equitable standing to pursue equitable relief, which is an injunction....She doesn't precisely discuss what law she was applying. I think you could read the whole opinion as she's applying corporate law in some sense, not necessarily specifically Delaware law....Maybe the parties didn't really argue that point, maybe they didn't point to which law applied. But...she found equitable title for standing purposes based on the corporate relationship, the exercise of control, specifically over patent licensing and enforcement, not just control overall the subsidiary.*"

C. Cross-Examination

1. Purpose of Patent Statutes

574. Asked by counsel for Teva what it is that patent statutes provide for (the issues that they provide for), the following exchange occurred between Prof. Chisum and counsel for Teva:

Prof. Chisum:	*Patent statutes provide for the conditions of patentability that you must meet to get a patent. They provide for the procedures of timely filing of applications. They regulate what the Patent and Trademark Office does. They provide for the issuance of patent and what the rights that are conferred by the statutes are and what the remedies for infringement of the patent are.*
Counsel:	*And they provide for...priority, isn't that correct?*
Prof. Chisum:	*They provide for priority in the United States....Not the type of priority you're talking about in this case....*

2. Section 118

575. Asked about §118, the following exchange occurred between counsel for Teva and Prof. Chisum:

Counsel:	*And as of this time, the §118 provision that reference was made to in your evidence, that precluded anybody other than the inventor applying for a patent, except in the limited circumstances of death, isn't that correct? ...*
Prof. Chisum:	...[T]*here is an earlier statute that provides for filing an application by one who is authorised to do that. And then 118 deals with filing...whether you do it in the name of the inventor or* [otherwise]....
Counsel:	*But the intent of that statute was except in those rare circumstances, it would be the inventor who was the legal owner of the patent?*
Prof. Chisum:	*Correct.*
Counsel:	*Who would apply for it, isn't that correct?*
Prof. Chisum:	*Yes.*

3. *Erie*

576. Asked whether the question of patent infringement is dealt with in the federal courts, Prof. Chisum indicated that this was so. Asked about the decision in *Erie* and its relevance to the case at hand, the following exchange occurred between counsel for Teva and Prof. Chisum:

Counsel:	*What is the...broad principle in the* Erie *case? ...*
Prof Chisum:	*There's no general federal common law....*
Counsel:	*What was the principle on which that was stated?*
Prof. Chisum:	*Because there's no statute enacted by Congress specifically dealing with those torts....*
Counsel:	*Exactly. There was no statutory intervention by Congress and there was no basis in the Constitution, isn't that correct?...*
Prof. Chisum:	*There is not a Congressional intervention into the traditional issues of property ownership.*
Counsel:	[Here] *there is a Congressional intervention in relation to the subject matter of patents and a constitutional basis, isn't that correct? ....*[I]*t intrudes significantly in the area of patent law and the patents themselves are a creature recognised in the Constitution and...*[f]*ederal statute?*
Prof. Chisum:	*Patents are a creature of the federal statute if they're created properly, yes.*
Counsel:	*And I take it...you would regard that as an important distinction between the subject matter of this case and the issue that arose in Erie?*
Prof. Chisum:	*I don't see the important distinction.*

4. Section 261, Standing, and Ownership

577. In response to a succession of queries from counsel for Teva, Prof. Chisum agreed that (i) the requirement in §261 of having an assignment in law by writing was a federal intervention dealing with a requirement for legal assignments, (ii) if a person attempts to transfer legal title and does not do so by writing, then there is generally no valid assignment, (iii) if a person has no valid assignment and comes to sue somebody, the court will say that absent a valid assignment, there can be no suit. Following on this last point, the following exchange took place between Prof. Chisum and counsel for Teva:

Prof. Chisum:	*They would say you have no standing....*
Counsel:	*...But in determining standing, they look at my ownership, isn't that correct?*
Prof. Chisum:	*Yes.*
Counsel:	*In order to determine standing, isn't that correct? ....They look at ownership, isn't that correct?*
Prof. Chisum:	*That's correct.*
Counsel:	*And when Prof. Thomas says, yes, of course those cases address standing, but in addressing standing, you necessarily must look at ownership, he's absolutely correct?*
Prof. Chisum:	*Yes.*
Counsel:	*...And, therefore, to talk about all those cases as being cases only addressing standing doesn't in fact give the complete picture, isn't that correct?*
Prof. Chisum:	*Well, to the extent that they discuss ownership...they do* [so]*...as a matter of state law and, therefore, their view is subject to whether*

it's correct under the state law.

Counsel: *....What law they apply to the question of ownership is a distinct point, Professor, as you know. But they do have to address ownership, isn't that right?*

Prof. Chisum: *Yes....*

Counsel: *...With regard to the question of ownership, it is state law. But, nevertheless, it is the Federal Court determining what the law is and applying it to the particular case?*

Prof. Chisum: *Yes....*

Counsel: [T]*he federal courts have only recognised* [equitable] *ownership in certain contexts, isn't that correct?*

Prof. Chisum: *....And I tried to explain it is because they are addressing standing....But that's right.*

Counsel: *But you're not an expert in state law, you have told us that.*

Prof. Chisum: *Correct*.

Counsel: *You are here on the federal law. And in the federal courts...both Digitech and Beam Laser...made...clear the circumstances of equitable ownership that have been recognised by the federal courts.*

Prof. Chisum: *Yes.*

5. Some Cases As Considered in *Chisum on Patents*

578. Counsel brought Prof. Chisum to:

– his consideration of *Frugoli* in *Chisum on Patents* and to the related observations that: "*The only way title to a patent may be transferred is by way of assignment*" and that *"[A]ssignment is the only concept recognized by 35 USC... by which one can transfer his rights in a patent.*"

– his consideration of In Re CFLC, Inc., 89 F.3d 673, 679 (9th Cir. 1996) (or Everex Systems) and the Stanford University case and the related observations that:

> "*The assignability of patent licenses is governed by federal law, even where the contract at issue would generally be governed by state law*", "*A nonexclusive patent license 'cannot be assigned unless the patent owner authorizes the assignment or the license itself permits assignment*" and "*The assignability of licence must be expressly stated in the contract at issue*", *and that* "*Federal law governs the assignability of patent licences because of the conflict between federal patent policy and state laws.*"

– the observations of the Ninth Circuit in *Everex Systems* that "*Federal patent policy...does justify the application of Federal patent law*", that

> "*The fundamental policy of the patent system to encourage the creation and disclosure of new, useful and nonobvious advances in technology and design by granting the inventor the reward of 'the exclusive right to practice the invention for a period of years'. Allowing free assignability or more accurately allowing States to allow free assignability… of non-exclusive patent licences would undermine the reward that encourages invention because a party seeking to use the patented invention*

> *could either seek a license from the patent holder* or *seek an assignment of an existing patent…*"
>
> (an example of a federal court invoking policy in interpreting the scope of federal law), and that "*Federal law governs the assignability of patent licences because of the conflict between federal patent policy and state laws*".

579. Counsel for Teva then queried whether Prof. Chisum would agree with the proposition that while state law governs ownership, the extent to which state law governs any issue is in itself determined by federal law. Professor Chisum indicated that he did not agree with this proposition. When counsel put it to Prof. Chisum that this was what seemed to be stated expressly in *Everex*, Prof. Chisum responded that he considered it a "[d]*ubious*" decision, an "*eyebrow raising decision*", and that he:

> "*question*[ed] *how relevant it is in light of the decisions of the Federal Circuit, upon which Prof. Thomas relies heavily....*[a]*nd every patent scholar and lawyer does and it* [the Federal Circuit] *unequivocally states ownership of patents is a question of state law....*[a]*nd I can't believe the Federal Circuit then would concur with the Ninth Circuit*",
>
> albeit acknowledging that he was unaware whether it has in fact been overruled.

580. Pressed again by counsel for Teva on the extent to which federal law determines the extent to which state law applies to patent issues, the following exchange took place between counsel and Professor Chisum:

Counsel:	*I made it quite clear it is federal law that determines the extent to which state law applies to patent issues. And that is indisputably correct as a matter of principle.*
Prof. Chisum:	*No.*
Counsel:	*And federal law has determined the role of state law in the context of ownership. Those are federal decisions that say state law will determine ownership, isn't that right?*
Prof. Chisum:	*They are federal decisions that say that, absolutely.*
Counsel:	*And it's not the state that determines the extent of its jurisdiction in this area, it's the federal courts that determine the extent of the state's jurisdiction?*
Prof. Chisum:	*I can't agree with that...*[T]*he Delaware Supreme Court would not say I have to defer to a Ninth Circuit, they would apply their law in a case brought in their courts.*
Counsel:	*I'm not asking you now about this decision particularly....It's a general proposition. Of course state courts apply federal law where appropriate....*[b]*ut in drawing the line between whether federal law should apply to an issue governed by federal law, like patents...it's the Federal Courts that determine the dividing line?*
Prof. Chisum:	*Ultimately it's the Supreme Court that determines that dividing line....*
Counsel:	*....But it's a matter of federal law if it's being dealt with by the Supreme Court..?*
Prof. Chisum:	*In a sense, yes.*
Counsel:	*So, the answer to my simple question was federal law...determines the scope of the applicability of state law in this context?*
Prof. Chisum:	*In a sense...yes.*

6. Limited Value of US District Court precedent?

581. Counsel brought Prof. Chisum next to *Maquet*, a decision of the US District Court in which the court stated that it was "*wary of extending the doctrine of equitable title to situations where a corporate parent exercises control over a patentee subsidiary.*" This brought about an exchange between counsel and Prof. Chisum which had obvious ramifications for the extent to which reliance may be placed on *Hologic*. It is worth quoting this exchange in a little detail given its potential implications. I take up the exchange from a few moments after counsel for Teva had just read aloud the just-quoted words from *Maquet*:

Counsel:	...[T]*hat is a proposition that has not been overruled, isn't that correct? ...*
Prof. Chisum:	*....District Court cases carry very little precedential value....I mean, I have stopped citing them probably 20 years ago....Because of the dominance of the Federal Circuit. But I've even asked District Court Judges, you know, even within a district, they don't always follow their colleagues' decisions....*
Counsel:	*Do you remember you were asked about the Hologic case?*
Prof. Chisum:	*Yes.*
Counsel:	*And do you remember you identified its relevance? That's a* [US] *District Court* [case]*...isn't that correct?*
Prof. Chisum:	*....Yes.*
Counsel:	*And when you were referred to that and commenting on it, did you tell this Judge that the District Court's cases carry very little precedential value? Did you tell the Judge that?*
Prof. Chisum:	*I don't think I did....I don't think I gave it huge value either.*
Counsel:	*Well you didn't say, in answer to the question, this has little value, this decision. You didn't say that?*
Prof. Chisum:	*I was just trying to explain...the decision....*
Counsel:	...[A]*re you familiar with the cases that are recited in Hologic? ...*
Prof. Chisum:	...[N]*o, I don't think I went and read those cases.*
Counsel:	*No..?*
Prof. Chisum:	*No.*
Counsel:	*And if you were to attach any weight to a decision...you would look at the authorities that are cited in the case as part of the reasoning, is that correct?*
Prof. Chisum:	*If I was going to rely heavily on the case, I would, yes.*
Counsel:	*So, the Court can take it you don't place any reliance on Hologic?*
Prof. Chisum:	*I'm not sure whether I cited or relied on Hologic or not. No.*
Counsel:	*I'm asking you, are you relying on it or not?*
Prof. Chisum:	*Not really, no....*
Counsel:	*So, the judge can ignore that decision?*
Prof. Chisum:	*I wouldn't tell the Judge to ignore it. I wouldn't presume to tell a Judge to ignore.*
Counsel:	*Okay. Well, you are a very polite man, Professor, and probably absolutely correct.*

7. *Everex Systems* and Assignment of Patents

582. Responding to a question from counsel, Prof. Chisum confirmed that §261 specifically mentions the assignment of patents and does not mention the assignment of licences. Counsel then noted that it is in *Everex* where one finds the Ninth Circuit stating that the assignability of patent licenses is governed by federal law, suggesting that, as a consequence, "*even in respect of*

assignment of licences, federal law is saying what can and cannot be recognised, isn't that correct?" Professor Chisum agreed that this was what the Ninth Circuit had said in this case. The following exchange then ensued between counsel for Teva and Prof. Chisum:

Counsel:	*And, therefore, when state law decides ownership in the cases which have been identified, the extent to which state law intervenes, as you've agreed, is itself a matter of federal law?*
Prof. Chisum:	*Say that again? I'm sorry.*
Counsel:	*Whilst state law governs the ownership issue....*[t]*he role that can be played by state law in these patent matters is, as you have agreed, determined by federal law?*
Prof. Chisum:	*I think I have agreed to that in a broad sense.*

8. *Dalzell*
'Hired to Invent' and 'Shop Right' Doctrines

i. 'Hired to Invent' Doctrine

583. Counsel for Teva referred Prof. Chisum to the observation of Gray J. in *Dalzell* that *"An oral agreement for the sale and assignment of the right to obtain a patent for an invention is not within the statute of frauds, nor within section 4898 of the Revised Statutes"*, and then refers to four further cases. Asked what those cases were concerned with, Prof. Chisum could not recall in detail but indicated that "*they involve...alleged oral contracts*." Counsel thereafter brought Prof. Chisum to the observation in *Chisum on Patents* that:

> "*The law regarding implied contracts to assign patent rights in the employer/employee context has developed primarily in two areas: where the employee is hired for some particular reason and where the employee holds a position of trust as to the employer.*
>
> ...
>
> *Rather than considering all the circumstances in finding contract terms implied in fact, the hired-to-invent doctrine employs a bright-line rule that a contract term transferring invention ownership to an employer may not be inferred when the inventor is an independent contractor*."

584. Counsel for Teva then put it to Prof. Chisum that what one can see in the foregoing is federal law determining the extent to which the 'hired to invent' doctrine can be applied. When Prof. Chisum responded that "*these are all state law matters*", counsel noted that the authority that *Chisum on Patents* itself cites in this regard is a federal case.

ii. 'Shop Right' Doctrine

585. Counsel for Teva moved next to explore the consideration in *Chisum on Patents* of the 'Shop Right' Doctrine, the following exchange ensuing between counsel and Prof. Chisum in this regard:

Counsel:	*And that doctrine is slightly distinct. It's the doctrine that provides that an employee who uses his employer's resources to conceive of an invention etc., they get a mandatory licence that's not exclusive, I think, isn't that* [correct] –
Prof. Chisum:	*Yes.*
Counsel:	*And that's been developed at a federal level as well, isn't that correct?*
Prof. Chisum:	*Well, it's applied...as a defence to patent infringement....*
Counsel:	*But it's a doctrine that's been developed at a federal level, isn't*

that correct? It's part of federal law?

Prof. Chisum: *No, I wouldn't say it's part of federal law. Because it deals with the relationship between an employer and employee.*

Counsel: *But if it's a defence to an infringement action, it must be developed at a federal level.*

Prof. Chisum: *Well, it must be applied as a federal matter....*[b]*ecause patent infringement suits are within the exclusive jurisdiction of the federal court. That does not mean every issue of law that it applies in the course of the suit is...*[f]*ederal law.*

iii. Return to *Dalzell*

586. At a later point in the cross-examination, counsel for Teva again returned to *Dalzell*, the following exchange taking place between himself and Prof. Chisum:

Counsel: *Professor Thomas said clearly in evidence, firstly...*[that] Dalzell *was an 'employed to invent' case....*[and] *secondly...that the subsequent interpretation is that an...express or implied oral contract was sufficient to effect...an assignment in equity. He said that very clearly....*

Prof. Chisum: *I just don't see where he gets out of the broad statement by the Federal Circuit that says ownership is a matter of state law....*[that] *'oh, but they don't mean it, they only mean ownership in the employed context'.*

587. Asked if it was (as is stated in *Chisum on Patents*) "[t]*he prevailing view...that ownership rights in patents arising out of an employment relation are governed by state law*", Prof. Chisum agreed that this was so. Asked whether this was "*a view expressed and decided on the basis of federal law*", Prof. Chisum indicated that it was "*in...*[the] *sense that we've gone through several times.*"

9. Federal Policy

588. Counsel referred Prof Chisum to the section of *Chisum on Patents* where the following is stated:

> "*State law rather than federal patent law, generally governs ownership rights in patentable inventions, including the rights as between an employer and employee and state law must yield only when it would create a serious conflict with Federal patent policy"*,

and asked whether it was not clear from the case-law to which counsel had brought Prof. Chisum, and from Prof Chisum's own treatise "*that federal policy is relevant in determining the scope of federal law*". Professor Chisum agreed that this was so but that "*in this particular area of ownership of patent rights...the law* [is]*...clear that state law applies.*" He noted that Prof. Thomas has canvassed the argument that a uniform federal rule would work better for policy reasons but noted (again) that "*what the case law, including the Federal Circuit, consistently says...is that state law governs ownership, even though that means it's going to vary from state to state.*" Professor Chisum added too that while, in his evidence, he has given "*a lot of weight to older cases*", *Schwendimann* is a decision of the Federal Circuit from 2020 which again offers "*clarification that state law applies to ownership....[a]nd it distinguishes...anything to the contrary.*"

10. *Top Victory*

589. Counsel brought Prof. Chisum to the decision in *Top Victory* and asked whether this was not

yet another example of the Federal Circuit deciding the circumstances in which one can have equitable ownership. The following exchange then occurred:

Prof. Chisum:	...[T]*hat's...equitable ownership for standing purposes.*
Counsel:	*But there's not two different forms of equitable ownership, is there?...There's equitable ownership, full stop?*
Prof. Chisum:	*As determined by state law.* [I understand this to mean 'Yes, that is so, with the notion of equitable ownership being determined by state law']. *But then there is the question of standing and the...Federal Circuit hasn't fully sorted out to what extent equitable title should be sufficient...to meet the standards for standing.*"

11. *Beam Laser*

590. Counsel brought Prof. Chisum next to the decision in *Beam Laser* and to the observation in footnote 6 to the decision of Smith J. that "*The only cases from the Federal Circuit recognizing an equitable title to a patent, of which the court is aware, involve a contractual arrangement between the party claiming to hold equitable title.*" This led to the following (by now predictable) exchange between Prof Chisum and counsel for Teva:

Prof. Chisum:	...[A]*s I think I tried to explain before, it's recognising equitable title to support standing, which as I say, is not clear from the statutes that that's proper.*
Counsel:	*But all these cases are federal cases dealing with the concept of ownership, admittedly in the context of standing.*
Prof. Chisum:	*Yes.*
Counsel:	*But nevertheless, identifying what ownership is recognised for patent law purposes, isn't that correct?*
Prof. Chisum:	*They do refer to title....They don't say that it's not controlled by state law, they say the reverse, they say it is controlled by state law.*

12. *Spine Solutions*

591. Counsel turned next to the decision in *Spine Solutions.* That case, it will be recalled, is authority for the proposition that, even in the context of a licence, some understanding between related companies is not sufficient to create an exclusive licence. The following exchange then arose between counsel for Teva and Prof. Chisum:

Counsel:	...[J]*ust so far as the broader principle is concerned, an understanding isn't sufficient to create an exclusive licence....*[W]*ouldn't it follow that an understanding is insufficient to create an assignment?*
Prof. Chisum:	...[I]*t wouldn't be sufficient if it wasn't in writing to create an assignment of legal title. Whether it was sufficient...to create an equitable title is ultimately a question of state law....*
Counsel:	*But this is the United States Courts of Appeal, Federal Circuit....*[a]*nd it is saying, it's not saying this is a matter of state law, it is saying* [that] *an understanding is not sufficient even for the purpose of the transfer of an exclusive licence. Isn't that correct?*
Prof. Chisum:	*It's correct. For the purposes of –*
Counsel:	*And it doesn't refer to state law...*
Prof. Chisum:	*I don't believe they refer to state law, no.*
Counsel:	*No. And it would follow that, in the context of an assignment of a*

patent itself, it would be the Federal Circuit that would determine it and an understanding about a transfer would be insufficient; that would follow, wouldn't it?

Prof. Chisum: *It would follow* [that] *they would follow state law, as they have said explicitly.*

Counsel: *Professor, you agreed that they determined whether there was an assignment of an exclusive licence on the basis of an understanding as a matter of federal law.*

Prof. Chisum: *But as a matter of standing...*[T]*hey didn't discuss state law in either direction....*

Counsel: *And they didn't...say it's a matter of state law. They said, 'no, this doesn't arise'?*

Prof. Chisum: *Right, yes.*

Counsel: *And I know you draw the distinction between standing, but we had earlier this morning, and you agreed with me that the question of standing was based on ownership. And all of these cases are determining whether somebody is an owner or not, isn't that correct?*

Prof. Chisum: *Yes....And we know what they say as to how you determine ownership. You determine it by looking at state law.*

Counsel: Yeah. *And there is no freestanding determinations or concepts of ownership in the patent area separate from these cases?*

Prof. Chisum: *There's what?*

Counsel: *There's no second meaning for ownership. These cases are determining, in the context of patents, admittedly against a background of standing, what is or is not ownership?*

Prof. Chisum: *I don't think that there's two consents* [*sic* – 'concepts'] *of ownership. There is a concept of ownership, yes.*

13. *Site Microsurgical Systems*

592. Counsel turned next to the decision in *Site Microsurgical Systems* and the observation therein that the Patent Code provides that the term 'patentee' "*includes not only the patentee to whom the patent was issued but also the successors in title to the patentee*" and also that "*The patent laws specifically provide for the transfer of rights.*" Having read these extracts aloud, counsel put it to Prof. Chisum that "[i]*n other words, the transfer is governed by federal law*", that:

> "[T]*he way it works is...you have to have an assignment and for it to be in law it's an assignment in writing. And they* [the courts] *will look, as Prof. Thomas said, as to whether there are words of assignment there....*[b]*ut leaving it, if it is an assignment, to state law to determine whether ownership has successfully transferred. I think that's a fair statement?*"

593. Professor Chisum responded that "*I think that's right, but....state law determines whether there has been a transfer of ownership*."

14. *Schwendimann*

594. Counsel brought Prof. Chisum next to *Schwendimann* and suggested by reference to same that "*the threshold* [for §261 purposes] *is 'is there an assignment?' And if there is something that constitutes an assignment, the issue of ownership is then determined by state law*". In response, Professor Chisum indicated that he "*would characterise* [the position as being that] *there is this requirement of a written instrument....[a]nd then there is the requirement of ownership....*[a]*nd ownership is determined by state law.*"

15. *Solomon*

595. Counsel brought Prof. Chisum next to the decision in *Solomon*, a Ninth Circuit case, in which it is stated that "*A patent is a creature of federal statute and may be transferred only according to the terms of the patent statutes*". Asked whether it was his position that he did not demur from this statement, Prof. Chisum responded as follows:

> "*I demur pretty much....for several reasons, I would say no court would take at face value the broad reading* [in *Solomon*]*....I will explain [the case] just a little bit. It's...not a patent case as such, it was a criminal prosecution against defendants who were alleged to be committing tax fraud. And the fraud consisted of* [representing]*...to...investors that they were buying patents and then you could get certain write-offs from that fact. Well, it turns out they...had not really purchased as many patents as they represented. And the defendants said, 'oh, but we had oral commitments from inventors'....And you can definitely read the Ninth Circuit's opinion here to say that...an oral agreement to transfer a patent is totally unenforceable because of patent law in 261. So, on that broad reading...that's against my position. I think that's wrong. But there's about...three or four reasons that I don't think the courts would follow that....*[and] *I don't think the Ninth Circuit would follow it if they were better informed.*
>
> *The first...is it's an alternative holding. Because they go on to say, well, even if it was enforceable, it was still a fraud, because the tax laws required that there be...legal title ownership...to get the tax deductions. So, you can say they could have decided the case on that basis.*
>
> *Secondly, they don't cite cases like Dalzell and other authorities about...enforceability and equity, which wasn't directly the issue - remember, this is a criminal fraud case.*
>
> *Another* [third] *reason is this is the Ninth Circuit again....But I agree...in fairness, one could argue that that statement, broadly construed and disregarding the alternative reading and all the history and the way the Federal Circuit tends to read 261* [in a manner that favours the position of BMS]*....But I have to say a well-informed court would not follow that broad direction....*
>
> *And in particular* [this is a fourth reason why the decision would not be followed] *they don't cite the Supreme Court's Dalzell case, which said at least, in some circumstances, an oral agreement relating to the transfer of rights and invention are enforceable. So...here you've got a Court of Appeals case that's contrary to a Supreme Court* [decision]."

596. Counsel for Teva next drew the attention of Prof. Chisum to the observation in *Chisum on Patents* whereby "*you were citing this as authority....for* [the following]: '*In the context of an assignment of a patent, the parties can agree verbally until the cows come home and that patent is not assigned unless there is a writing*' [this was actually a paraphrase of the applicable judicial observations]. The following exchange then ensued between counsel for Teva and Prof. Chisum:

Counsel	*Section 261 is applicable not just in standing cases, it's applicable in respect of applications for patents, isn't that correct?*
Prof. Chisum:	*Not exactly, no....I mean, it's not limited to standing....*[I]*t applies to whenever you're assigning legal title....*[an] [a]*ssignment at law....To a patent application or a patent....*
Counsel:	*And, therefore, §261 is relevant in respect of applications and...in respect of priority, isn't that correct? ...Because the Patent Code, in determining priority within the US, does it on the basis of legal title, isn't that correct?*

Prof Chisum:	*I don't think that's the case....If you had an inventor who filed an application and...has already contracted away legal title...*[and] *within a year files a follow-up application in the US, that would be a valid -*
Counsel:	*That's where the inventor does it....*[A]*bsent an application by the inventor, the priority is determined by the legal title, isn't that correct?*
Prof. Chisum:	*I don't think that's true, no....*
Counsel:	[Y]*ou don't know whether priority outside the inventor situation is governed by legal title?*
Prof. Chisum:	*Maybe I don't know what you mean by 'governed by legal title'.*
Counsel:	*Well, determined by legal title.*
Prof. Chisum:	*You don't need legal title even to file an application.*
Counsel:	*That's because the inventor is specifically required to file....Isn't that correct? So, do you know the answer to my question?*
Prof. Chisum:	*I would have to re-check the statute. But I don't think* [outside the inventor situation that] *you need legal title*.

D. Re-Examination

1. Issues of Equitable Ownership Before Federal Courts

597. Asked by counsel for BMS, in what circumstances would a federal court find itself considering whether there was or was not equitable ownership, Prof. Chisum indicated that a federal court would consider this "*if there was an argument that there was equitable ownership under, for example, state law.*"

598. Asked in what circumstances it would fall to a federal court to be looking at that question, as opposed to a state court, Prof Chisum indicated that potentially it could arise in a standing case.

2. Section 261

599. Recalling that the first line of §261 states that *"Subject to the provisions of this title, patents shall have the attributes of personal property*", counsel for BMS queried what law governs ownership of personal property. Professor Chisum responded "*state law....*[o]*r the law of foreign countries as well.*" Asked whether a patent is an item of personal property, Prof. Chisum indicated that it is.

600. Asked at a later point in the re-examination what §261 has to do with applications for patents, Prof. Chisum indicated that it says that an application can be assigned but it does not govern, *e.g.,* who can file an application.

3. Federal Law and State Law

601. Recalling that counsel for Teva had posited that it is the federal system that decides when state law applies, counsel for BMS asked:

- what the federal courts have said about what law governs ownership of patents. To this, Prof. Chisum indicated that the federal courts have said "[e]*xplicitly*" and "*as clearly as you can that it is state law*".
- when this question comes before a federal court, is it always clear that the federal court is applying state law? To this, Prof. Chisum indicated that "*It might not be*", that "*I have read some decisions where you could say they are applying general notions of corporation law*"; however, Prof. Chisum agreed that, strictly speaking, they should be applying state law.

– if, in such an instance, a federal court does not apply state law and says something about equitable title, does that displace the applicable state law? To this, Prof. Chisum responded "*No*".

4. *Erie*

602. Asked what Brandeis J. seeks to convey in his 'third point' in *Erie* as to the impact, if any, of dicta of Federal Courts on a question that is actually governed by state law, Prof. Chisum indicated that "*he's saying that decisions of courts of the State are authoritative on the State's law....*[t]*hat is well understood....*[and that] *they* [the federal courts] *should apply the law as interpreted by the state's courts.*" Professor Chisum agreed when counsel for BMS put it to him that "*that doesn't stop federal Judges saying things, it just has an implication for what it means when they say things, isn't that right*?"

5. *Akazawa*

603. Counsel for BMS referred to the decision in *Akazawa*. There, Prof. Chisum recalled, (i) the case involved Japanese intestacy law and a situation in which a title owner in Japan had died and there were certain laws in Japan that dealt with how the property descended, and (ii) the Federal Circuit indicated that it could apply Japanese law to determine ownership, even as a matter of standing. When counsel put it to Prof. Chisum that the case "*didn't involve an assignment in terms of change of ownership*", Prof. Chisum indicated that this was so.

604. The significance of *Akazawa*, as I understand the wider evidence of Prof. Chisum, is that there the Federal Circuit specifically and expressly confirmed what, in truth, seems self-evident from the words of Section 261 itself, and that is that §261 does not apply to a change of ownership through any method other than by assignment.

6. *Steele*

605. Counsel for BMS referred next to the decision in *Steele*. That was a case where the US District Court found standing for one subsidiary but not another. In response to further questioning by counsel, Prof. Chisum agreed that this was a case where exclusive control of the patent yielded the requisite standing and that this was not a case where there had been any form of assignment in place.

7. *Spine Solutions*

606. Counsel for BMS recalled that counsel for Teva had "*used this case to say that an understanding between related companies was not sufficient to give equitable ownership*." Professor Chisum agreed, when it was put to him, that the court in that case found there to be no enforceable understanding between the parties.

8. *Beam Laser*

607. Counsel for BMS brought Prof. Chisum next to the decision in *Beam Laser*. Counsel for BMS also referred Prof. Chisum at this juncture to his own observations at §46 of his opinion where he states as follows:

> "46. *In paragraph 58 of the Thomas Statement, Professor Thomas asserts that I 'summarily' dismiss a 'long list of opinions holding that corporate parents do not hold equitable title in patents owned by their subsidiaries' because they 'primarily pertained to standing.' To the contrary, I carefully considered each case Professor Thomas cited and determined that they not only pertained to standing but also did not apply federal standing law to override a showing that a corporate entity had equitable title under state law…*".

608. Counsel for BMS then asked Prof. Chisum what was the main point that he had been making about the assessment of the above-mentioned cases that Prof. Thomas had relied upon. To this, Prof. Chisum indicated that "*The point was that none of these cases say 'state law recognises equitable title to that patent in these circumstances, however we're going to disregard that....*[b]*ased on federal law or policy. There's no case that says that, or even suggests that.*"

9. *Frugoli* v. *Fougnies, 2003 U.S. Dist. LEXIS 26551 (D. Ariz. 2003)*

609. Turning briefly to the decision in *Frugoli*, counsel for BMS noted that it had been put to Prof. Chisum that the Court in *Frugoli* was saying that the only way to transfer a patent was by assignment. Counsel queried whether Prof. Chisum considered whether that could be right. To this question, Prof. Chisum responded that "*it's clear that there are other ways to transfer, to assign a patent, such as by operation of law, like the intestacy case.*"

10. *In Re CFLC, Inc., 89 F.3d 673, 679 (9th Cir. 1996)* (or *Everex Systems)*

610. Counsel queried, in the context of the above-mentioned case, whether a decision of the Ninth Circuit is binding on the Federal Circuit. Professor Chisum indicated that it is not (the consequence, touched upon by counsel, being that *Schwendimann* was not overruled by *Everex/CFLC*. (I note in passing that *CFLC* was not mentioned by Prof. Thomas; however, Prof, Chisum was in a position to deal with it robustly.)

11. *Schwendimann*

611. Asked whether *Schwendimann* continues to be an authority of the Federal Circuit, Prof. Chisum responded, in the following terms, that it does:

> "*Schwendimann is very much, probably the most recent Court of Appeals case affirming that...state law regulates ownership issues. In fact it was really quite detailed. There was a flawed written assignment in that case and they said we can go to state law to resurrect the chain of title. So....a specific State's law can play a role in determining the ownership, even for legal title and even for standing.*"

12. Right to claim priority as a property interest

612. Counsel for BMS recalled that at the end of his cross-examination counsel for Teva had put it to Prof. Chisum that "*the ownership of priority, the right to claim priority...*[is] *in the legal owner.*" The following exchange then ensued between counsel for BMS and Prof. Chisum:

Counsel:	*...Is the right to claim priority an interest in a patent, or is it a property interest?*
Prof. Chisum:	*I think it would be, yes.*
Counsel:	...[W]*hat law governs that, Professor?*
Prof. Chisum:	*...State law.*

18

Some Conclusions

613. What key conclusions might be reached following a consideration of the evidence of Professors Thomas and Chisum. It seems to me that the following conclusions might safely be stated:

[1] in its opening written submissions, Teva asserted that United States federal law imposed a requirement of an instrument in writing before equitable ownership in US165 could pass to BMS Co. (Thus Teva's written opening submissions state at §4.16(f) that:

> "*BMS' theory of beneficial ownership overlooks the requirements of US federal law, which requires 'an instrument in writing' (35 USC §261) and BMS can point to none. That statute reflects a policy of legal and commercial certainty as regards the ownership of patents*."

Writing in this vein in his first report, Prof. Thomas states that "*In the absence of a written assignment, US courts have refused to allow companies related to the patent owner to claim either a legal or equitable interest in that patent because the companies are commonly owned*". In the witness-box, Prof. Thomas initially held to this view. Asked by counsel for BMS if he stuck by the view that the United States courts have required a written assignment before an equitable interest will be recognized, Prof. Thomas gave a one-word response, "*Absolutely*". But his view changed in the following exchange with counsel for BMS when they were treating with the *Spine Solutions* and *Dalzell* cases:

Prof. Thomas:	*Well, it's my understanding of the case that the fundamental fact that's being asserted here, that there's a chain of companies that have common ownership, that's the fundamental fact that matters. And the Court insists upon a writing, even for a licence.*
Counsel:	*But the Court doesn't say you need a writing, the Court doesn't say you need an assignment.*
Prof. Thomas:	*On the right column on page 292 the Court does note that there is no oral or written agreement. And that is dispositive.*
Counsel:	*Oral. Oral or written. You said that we need a written assignment.*
Prof. Thomas:	*Well, as we've gone through at great length, the* Dalzell *case does allow an oral agreement to assign. So, again, if there is an immediate assignment of a legal interest, that has to be in writing. An equitable assignment, an*

	executory one, could be oral or in writing. And I think the Dalzell case says that pretty clearly.
Counsel:	*But, Professor, when we were discussing* Dalzell*, you said that it only applied to inventor, assignments from inventors. I asked you specifically whether it was not authority that an oral agreement to assign was enforceable in equity and you said it's only restricted to employee inventors*.
Prof. Thomas:	*So, I said the facts of the case involved an oral agreement between the employed inventor and his employer - again, someone who had been hired to invent, provided facilities, there was a meeting of the minds that the rights to the invention would inhere to the employer. So, I was speaking to the facts of the case. Again, if counsel's suggesting that* Dalzell *has nothing to do with group companies, I agree with her.*
Counsel:	*I'm not suggesting that. I'm suggesting the opposite. I've been suggesting the opposite from the start. It is you who said that* Dalzell *has nothing to do with group companies, that it is not authority that group companies can have an oral agreement between themselves.*
Prof. Thomas:	*I don't really have any particular problem with evidence of an oral agreement between two parties, no matter who they are, to assign rights in the future. And that can convey an equitable interest. I'm not aware of any oral agreement that's been asserted in this case.* [Prof. Thomas is correct in this last sentence.] *And I would note in Dalzell the standards are quite high to show that.*

This evidence was surprising to me. Teva has consistently canvassed the view that §261 required an assignment from BMS Pharma to BMS Co before an equitable interest could arise in BMS Co. at the relevant time. And §261 refers applications for patent, patents or any interest therein, being assignable in law only by an instrument in writing. Yet, here was Prof. Thomas, Teva's expert on United States federal law accepting that an oral agreement would suffice and thereby conceding that §261 is not, and never was, the fatal flaw in BMS's reasoning that Teva has canvassed it as being. Prof. Thomas's evidence in this regard, with respect, drives 'a cart and horse' through the assertion by Teva in its written opening submissions (at§4.16(f)) that: "*BMS's theory of beneficial ownership overlooks the requirements of*

US federal law, which requires 'an instrument in writing' (35 USC §261) and BMS can point to none." For here was Prof. Thomas, Teva's own expert witness on United States federal law telling me that an oral agreement would suffice. And it makes no difference that no-one has sought to rely on an oral agreement in this case: the point is that it is Teva's logic, not that of BMS, which is flawed in this regard. All that said, all that I have just stated regarding §261 is without prejudice to the conclusion that I reach later below that in fact §261 does not apply to BMS's equitable ownership of US 165.

[2] as Prof. Chisum explained, it is a long-established principle in the United States that state law applies to the ownership of property, including intellectual property, and that the "*Federal Circuit has said it as clearly as you can that it is state law*".

[The brief extract from Prof. Chisum's evidence above likely does not do justice to the comprehensive and complete nature of his evidence in this regard, as the following exchange between counsel for BMS and Prof. Chisum shows:

Counsel:	*Now, what law governs ownership of personal property?*
Prof. Chisum:	*State law.*
Counsel:	*And what law –*
Prof Chisum:	*Or the law of foreign countries as well.*
Counsel:	*So, a patent is an item of personal property?*
Prof. Chisum:	*Correct.*
Counsel:	*It therefore follows that –*
Prof. Chisum:	*Yes.*
Counsel:	*- State law governs?*
Prof. Chisum:	*Yes.*
Counsel:	*Now,* [counsel for Teva]*...put to you that it was the federal system that's deciding when does state law apply.*
Prof. Chisum:	*Yes.*
Counsel:	*Now, what have the federal courts said about what law governs ownership of patents?*
Prof. Chisum:	*Federal Circuit has said it as clearly as you can that it is state law.*
Counsel:	*And has it said it in terms, Professor?*
Prof. Chisum:	*In terms?*
Counsel:	*In terms, has it said that explicitly?*
Prof. Chisum:	*Explicitly, yes.*]

(Professor Chisum was here referring to the case of *Schwendimann*, which in turn referred to *Enovsys*, *Jim Arnold*, and other federal authority, to the same effect. So his views in this regard were supported by authority.)

[3] Professor Chisum also noted that United States federal law applies by way of specific provision, with the result that anything not governed by federal law is governed by state law.

[This is clear from the following excursus on United States law provided by Prof. Chisum early in his cross-examination:

Counsel: *And I wonder whether, as a preliminary matter, you could just briefly outline how the two systems of law relate to each other, in general terms, not specifically on patents, but in general terms at this point?*

Prof. Chisum: *Okay, I'll try and be brief, your Honour. But the United States, of course, has a federal system of law in which, on the one hand, you have state courts and state law and you have Federal Courts and federal law. If I had to use any sort of general description of the relationship, I would say state law is the general, whereas federal law is always just the specific. And the same applies to the court system. So, if you take, you know, I was thinking of a metaphor, maybe this is handy, it may be useful or not, but if you thought of the whole body of jurisprudence as a big ocean, state law would occupy all the water, federal law would be particular islands.*

Judge: *Right.*

Prof. Chisum: *Sitting in – so, federal law comes into play generally when there is just a statute or a federal constitutional provision at issue. And I can't emphasise enough that in terms of all the relationships you think about, transactions and occurrences, the overwhelming percentage of them are governed by state law. That's kind of reflected in law school too. When you first go to law school, your first courses are on contracts and property, you know, and torts and criminal. Those are all state law areas. You don't have a lot of – the federal areas are all specialised. Now having said that, of course, you know, a very important federal item is the, you know, patent system. But as I say, state courts have general jurisdiction, which means they can entertain all kinds of cases. Hypothetically, just as an example, a Delaware pharmaceutical company could sue an Irish pharmaceutical company in the Delaware state courts, like some of the courts that Judge Chandler used to be on. That would be perfectly within their jurisdiction. And there's an appellate court system, you know, in the states. And importantly, under a system – if they applied Delaware law, the ruling of those courts, including by their Supreme Court becomes the definitive interpretation of that state*

law. Now we have, on the other hand, the federal court system. Those courts you would not describe as having any general jurisdiction. They only have jurisdiction if there's a specific statutory grant. And the two major categories, the most important is cases that arise under federal law, such as patent law, but other areas. And then they also have jurisdiction, something called diversity and citizenship. So, in my hypothetical, in the US company, Delaware corporation, sued the Irish, the Irish company could 'remove it' to federal court. The idea may be the federal courts would be less favoured towards the Delaware, you know, corporation. That was the theory. It goes back to the founding of the Constitution, that was provided in Article 3, which deals with the federal courts. So those are the only types of – and again, the state courts have general jurisdiction, but there is an exception, an important one, that certain areas are exclusively for the federal courts. And one of them is cases arising under patent law. But that's defined in terms of pretty narrowly. That is a suit for infringement of a patent, for example. And the Patent Act defines, you know, who has a remedy to sue. It has to be the patentee, which means somebody who has a legal title by assignment and that's tied into jurisdiction. So I know, for example, there's a lot of discussion between Prof. Thomas and myself about standing; well, you shouldn't get the impression that standing is some kind of formal requirement, it's a very important part of the Federal Courts' jurisdiction. So the federal courts often realise that...in our scheme, they are limited and they have to keep their power within their defined jurisdiction or otherwise they are encroaching on the predominance of state law. I hope that wasn't too long.]

[4] contrary to *Schwendimann* and the federal court authority referenced therein, the federal cases which Prof. Thomas relied upon in his report and in his oral evidence for the proposition that equitable ownership in patents cannot arise as between group companies without an assignment, were not dealing with the question of the law to be applied to the question of ownership of patents. Four points might be made about the cases relied upon by Prof. Thomas in this regard. First, they are all standing cases *i.e.*, cases in which the relevant court had to determine whether a party had standing to sue on a patent under §281 of the US Patents Act, which provision is concerned with standing of a 'patentee' – with the result that most of the said cases do not deal with equitable ownership at all. Second, to the extent that the cases are touted (if

they are touted) by Teva as applying some form of constraint as regards the circumstances in which equitable ownership of patents can arise, I note that where state law applies – as in the question of ownership of property – courts in the United States, including its federal courts, are obliged to apply state law.

[This is known as the '*Erie Doctrine*', following on certain observations (renowned, it seems, in the United States) that were made by Brandeis J. in *Erie Railroad Co v Tompkins* 304 US 64 (1938), at 78 & 79:

> "*Except in matters governed by the Federal Constitution or by Acts of Congress, the law to be applied in any case is the law of the State. And whether the law of the State shall be declared by its Legislature in a statute or by its highest court in a decision is not a matter of federal concern. There is no federal general common law. Congress has no power to declare substantive rules of common law applicable in a State, whether they be local in their nature or "general," be they commercial law or a part of the law of torts. And no clause in the Constitution purports to confer such a power upon the federal courts. As stated by Mr. Justice Field when protesting in* Baltimore & Ohio R. Co. v. Baugh, *149 U. S. 368, 149 U. S. 401, against ignoring the Ohio common law of fellow servant liability:*
>
> > *'I am aware that what has been termed the general law of the country -- which is often little less than what the judge advancing the doctrine thinks at the time should be the general law on a particular subject -- has been often advanced in judicial opinions of this court to control a conflicting law of a State. I admit that learned judges have fallen into the habit of repeating this doctrine as a convenient mode of brushing aside the law of a State in conflict with their views. And I confess that, moved and governed by the authority of the great names of those judges, I have, myself, in many instances, unhesitatingly and confidently, but I think now erroneously, repeated the same doctrine. But, notwithstanding the great names which may be cited in favor of the doctrine, and notwithstanding the frequency with which the doctrine has been reiterated, there stands, as a perpetual protest against its repetition, the Constitution of the United States, which recognizes and preserves the autonomy and independence of the States -- independence in their legislative and independence in their judicial departments. Supervision over either the legislative or the judicial action of the States is in no case permissible except as to matters by the Constitution specifically authorized or delegated to the United States. Any interference with either, except as thus permitted, is an invasion of the authority of the State and, to that extent, a denial of its independence.*'"]

Federal law only pre-empts state law where there is a conflict and the question of ownership of property in this case presents no conflict with federal law because federal law does not apply. Third, on a related note, there is no federal common law, *i.e.* the *dicta* of federal courts do not displace state law on matters governed by state law.

> [Again, this is the '*Erie* doctrine', with Prof. Chisum observing as follows in this regard:
>
> > *The* Erie *doctrine is the one that says that federal courts have to follow state court authority and that there is – in other words, before* Erie*, there was authority that there was a federal common law that actually was only applied - you know, I mentioned the diversity cases, you know.... In the old, old days, the old bad days, the* [federal] *court would, on a contractual dispute, they would say; I'm applying the general federal common law just how to interpret. In a diversity case, only in diversity cases. And the Supreme Court, in 1938,* [in *Erie*] *a major case, every law student studies, says; 'no, you know, even in diversity cases, you know, you get the jurisdiction, but you don't change the law. The law is the law of the State and the State Courts' decisions are binding'. So, major concept.*]

Schwendimann makes clear that the applicable law when determining the issues of ownership in the priority dimension of this case is the applicable state law, *i.e.* Delaware law. Fourth, none of the cases to which Prof. Thomas adverted in this regard overrode a State-law indication of equitable ownership. Thus, per Prof. Chisum, in his written statement (see Appendix 2):

> *37. Paragraphs 41-44 of the Thomas Statement discuss the Federal Circuit's 2010* Spine Solutions *decision. That decision noted that the only question in that case was whether a party was 'an exclusive licensee for purposes of standing.' The decision does not cite, discuss or repudiate any issue of state law. In passages Professor Thomas quotes,* Spine *noted that it was 'undisputed' that one entity was the 'sole owner,' that there was 'no agreement, either oral or written' with respect to a patent. The party asserted, at most, that there was an 'understanding' with the patent owner that it would have an exclusive right to practice the patent. That 'understanding' was not asserted to be one of ownership. It was 'at most' a bare license. Thus,* Spine *did not consider or reject any theory of equitable title based on the facts and the applicable state law.*
>
> ...
>
> *46. In paragraph 58 of the Thomas Statement, Professor Thomas asserts that I 'summarily' dismiss a 'long list of opinions 'holding that corporate parents do not hold*

> *equitable title in patents owned by their subsidiaries' because they 'primarily pertained to standing.' To the contrary, I carefully considered each case Professor Thomas cited and determined that they not only pertained to standing but also did not apply federal standing law to override a showing that a corporate entity had equitable title under state law. The decisions held that a corporate entity lacked standing because it did not possess legal title via a Section 261 assignment in writing. Some, such as* Beam Laser *(2000), and* Steelcase *(2004), ruled that a parent corporation failed to establish that it had 'equitable title' to patents to which a subsidiary held legal title such as would support standing to seek equitable remedies. In* Beam Laser*, the district court did not cite or consider any asserted provision of state law supporting such title. Had the parent done so, the district court would have been bound to apply that law, as the Federal Circuit confirmed in* Schwendimann *v.* Arkwright Advanced Coating*, 959 F.3d 1065 (Fed. Cir. 2020), discussed above. In* Steelcase*, the district court carefully considered the facts and found standing for one subsidiary but not another.*"

[5] although the federal courts have the ultimate say in determining whether or not a particular matter falls to be governed by federal law or state law, the *Erie* doctrine and the principle of pre-emption continue to apply. However, the significance of this observation is lessened in the context of the present proceedings because the federal courts have in fact spoken on the precise topic of the law to be applied to ownership of patents and (as I have already touched upon above) have decided – in *Schwendimann* and the cases cited in *Schwendimann* – that the question of ownership of patents is a matter for state law.

[6] in its written opening submissions (at §4.16(f)) Teva refers to a general "*policy of legal and commercial certainty as regards the ownership of patents*" as justification (as I understand matters) for the proposition that BMS Co's equitable ownership of US 165 under Delaware law should not be entertained in this case. This, if I might respectfully observe, is a self-serving argument which, as BMS has pointed out in its written submissions, is inconsistent with Teva's argument before the Board of Appeal in Case T 205/14, a case brought by Teva itself where Teva asked the EPO to recognise a right of priority on the basis of equitable title and succeeded in fact, under Israeli law, on something that was less than legal title.

[7] on a related note, Prof. Thomas observes, in his second written witness statement (see Appendix 14) that "*The proposition that property rights should be orderly and predictable cannot be gainsaid*". But there are limits even to that proposition, for if it were applied to ban the vesting of *any* interest other than a legal interest, that would render the law of equity redundant.

[8] Professor Thomas drew a parallel between eligibility to file and standing to sue, suggesting that the law in both circumstances was the same. Thus, he suggested in his oral testimony, when it comes to "*standing to sue in federal court, but also standing to be able to file a patent application*", it is important to have the right entity "[b]*ecause the policy concerns are the same and so's the law*". However, the law, with respect, is not the same: it is clear from the evidence before me that standing to sue on a United States patent and eligibility to apply to register a United States patent are governed by

particular provisions of the United States Patents Act. The only provision concerned with ownership is §261 and, for the reasons set out later below in this chapter, §261 does not apply to BMS's equitable ownership of US 165.

[9] as I understand his written and oral evidence, Professor Thomas appears implicitly to accept that BMS Co. had equitable ownership at the relevant time, given his acceptance that BMS Co. had a right to call for the assignment to it of the relevant rights. Thus:

(i) in his first report, Prof. Thomas observes as follows:

> "39. *Based on the information in the Documents, there is no purported tangible form of an assignment. The only information relied on is a supposed internal policy of patent ownership in an internal BMS Company email chain in October 2001. These showed that BMS Company had a right to call for such a transfer. There is no evidence or statement to support the proposition that this right was ever exercised prior to the filing date.*",

and

(ii) in the course of his oral testimony, the following exchange occurred with counsel for BMS:

> "Counsel: *The second issue that I just want to air before we go into the cases is that is discussion of federal law constraints on equitable ownership, when equitable ownership will be recognised, is that not redundant, in circumstances where you appear to accept, in your report, that there was an equitable interest in this case in BMS Co? And I'll bring you to paragraph 39 of your report* [the paragraph quoted immediately above]....*Is that not the definition of an equitable interest?*
>
> Prof. Thomas: *I'm not – I do not believe there's any case in this bundle that uses the phrase 'right to call' and equates that with an equitable interest. It's true that an equitable title holder – in a sense the only thing an equitable title holder gets is the ability to compel transfer of legal title. But once more, that's never been exercised and the Federal Circuit has never recognised that in the case of group companies. Again, it is a contractual matter only. And that's the distinction that's relevant with respect to this paragraph.*
>
> Counsel: *But no one is saying that an equitable interest is the same as a legal interest.*

But what the equitable ownership gives you is the right to perfect your title by requiring the assignment to you?

Prof. Thomas: *I agree that as a general matter, when it applies, that an equitable interest would give you the right to compel transfer of legal title.*"

[10] it does not appear that §261 applies to BMS's equitable ownership of US165; I reason through why this is so below:

(i) as worded, §261 expressly provides that "*Applications for patent, patents, or any interest therein, shall be assignable in law by an instrument in writing.*" The notion that §261 imposes a writing requirement for an assignment in law of a patent was confirmed by Professor Chisum in the course of his oral testimony:

Counsel (BMS): *So, can you tell the Court what you say are the specific impacts of that section* [§261]?

Prof. Chisum: *Well, it is, by this longstanding interpretation, it means that if you are assigning, you know, in law, meaning you're assigning legal title, it's by an instrument in writing. So, it is dealing with assignments of legal title, assignments at law and not, for example, in equity....*[T]*here are cases, you know, if you actually read the statute, it says they are assignable this way, they don't exclude them being assignable in other ways. But it is actually read to mean if you're talking, at least in the standing cases, to mean if you're needing to rely on a chain of legal title, there is a writing requirement. But of course, they've also recognised, I think Prof. Thomas must have talked about it, in cases like inheritance working as a matter of law. And so it's not really clear that this is the only way for legal title to be assigned. What is clear is that it doesn't, going all the way back to Dalzell and all that history, it doesn't affect equitable enforcement of obligations defined by state law, however defined by state law*.

(ii) as described by Prof. Chisum, the Federal Circuit in *Schwendimann* dealt with the requirements of §261 in the context of what was required to have the status of patentee for the purposes of standing to sue under s 281 of the US Patents Act. The Court characterised the requirement as a requirement for an instrument in writing, imposing no form or content requirements and independent of the question of legal title which was governed by state law:

Counsel (BMS):	[Re. *Schwendimann*]. *I wonder could you comment on what you think the Court is there saying in respect of the relation of the requirement of an instrument in writing with the assessment of ownership of a patent?*
Prof. Chisum:	*Well, I think it means pretty clearly what the Court says, that is Section 261 imposes a written instrument requirement. But it doesn't -- and that is a matter of federal law for standing purposes at least. But you also, additionally, one and two, the two is you have to have legal title and that is a question of state law.*

(iii) Professor Chisum also gave evidence that §261 has no application where ownership of a patent changes other than by assignment:

Counsel (BMS):	*Just then one more general point in relation to how Section 261 does or does not apply. Could you just comment on what, if any, impact Section 261 has where the interest is acquired other than by assignment? So, if you're saying you've got an interest in a patent other than through assignment, does Section 261 apply at all?*
Prof. Chisum:	*Well, if I understand your question, assignments of other interests, or...*
Counsel:	*No, a change of ownership.*
Prof. Chisum:	*Right.*
Counsel:	*Other than through assignment. Did...Section 261 apply?*
Judge:	*So, succession would be an example.*
Prof. Chisum:	*No.*
Counsel:	*Succession would be an example.*
Prof. Chisum:	*No.*
Counsel:	*Your answer was "no". Thank you, Professor.*

(iv) following quite extensive discussion of *Dalzell* it is clear that §261 has no application to oral agreements to assign patents which are specifically enforceable without an 'instrument in writing'. In this regard, Prof. Chisum states as follows in his written report:

> "*19. There is no requirement that a specific written assignment is necessary to convey equitable title to an invention, a patent application, or a right to claim priority based on a patent application. Over a century ago, the United States Supreme Court stated: 'An oral agreement for the sale and assignment of the right to obtain a patent for an invention is not within the statute of frauds, nor within [the statute] requiring assignments of patents to be in writing; and may be specifically enforced in equity, upon sufficient proof thereof.'* Dalzell *v.* Dueber Watch-Case Mfg. Co., *149 U.S. 315, 320 (1893).*
>
> *20. The 'statute' requiring assignments 'to be in writing' the Supreme Court referred to in* Dalzell*, Revised Statute Section 4898, was the predecessor to the current assignment statute (35 U.S.C. § 261). Thus, the Court's holding in* Dalzell *establishes that a written assignment of a patent right is not necessary for a conveyance of equitable title. Consistent with* Dalzell*, Section 261 has never been applied in a case involving a dispute over ownership of a patent priority right (as opposed to ownership for purposes of standing to sue for infringement of a patent).*"

I am mindful that in his oral testimony, Prof. Thomas:

(i) said that §261 governed questions of substantive ownership on the basis that ownership does not transfer without an assignment. In his written evidence Prof. Thomas seems to take a more benign view of §261, stating as follows, at §37 of his first witness statement:

> "*The statute does not stipulate the form or the contents of the written instrument, and courts have held that this statute 'imposes minimal requirements for such* [an*] assignment.'* Software Rights Archive LLC *v.* Google Inc., *No. CIV.A. 2:07-CV-511, 2009 WL 901361, at *4 (E.D. Tex. Mar. 31, 2009).*"

(ii) read the Federal Circuit *dicta* in *Akazawa* on the non-application of §261 to changes of ownership other than by assignment, as being limited to changes of ownership occurring by 'operation of law' (though I respectfully note that the deciding court expressed no such limitation), and (iii) took the position that although §261 did not apply to equitable ownership arising from oral agreements to assign, it applied to equitable ownership arising in other ways. Having regard, however, to all of the foregoing it seems to me that in circumstances where (i) the Federal Circuit has said that s 261 does not apply to changes of ownership other than by assignment, (ii) the United States Supreme Court has said that §261 does not apply to equitable

ownership arising from oral agreements to assign, (iii) it would be contrary to logic and law (both United States court precedents and the express wording of §261 which refers to an assignment of a patent "*in law*") were I to conclude that §261 could somehow apply to equitable ownership arising other than through assignment; it is clear, as a matter of United States law, as described in the evidence before me, that it does not so apply.

[11] in his written evidence, Prof. Thomas appears to canvass, by reference to the *Leland Stanford* case that ownership of patents is a mixed question of federal and state law.

[Thus, in his first written report Prof. Thomas states as follows:

> "*31. Notwithstanding the general applicability of state law to questions regarding ownership of property and the interpretation of contracts, federal law governs the way in which an assignment of patent rights (including the right to claim priority) can be made.*
> *32. The leading case in this area,* Board of Trustees of the Leland Stanford Junior University *v* Roche Molecular Systems, Inc, *583 F.3d 832,841 (Fed. Cir. 2009), aff'd, 563 U.S. 776, 131 S. Ct. 2188, 180 L. Ed. 2d 1 (2011), summarized the situation as follows:*
>
> > *'*[T]he question of who owns the patent rights and on what terms typically is a question exclusively for state courts ... However, this rule has exceptions; the question of whether contractual language effects a present assignment of patent rights, or an agreement to assign rights in the future, is resolved by Federal Circuit law.*'*
>
> *33. There is therefore an overlap between state law and federal law regarding the transfer of patent rights and the two must be considered together in order to determine whether a particular purported transfer of patent rights is valid….*
> *34. Any transfer of the rights in present or future inventions or in or under present or future patents or patent applications under US law is governed by the combined effect of: a. the state law of the agreement by which the rights in the same are said to be transferred; and b. Federal law.*"]

However, Professor Chisum confirmed in his oral testimony that the Federal Circuit, in *Leland Stanford*, adopted the view that the question of whether *future rights* were assigned or had merely been agreed to be assigned should be decided by the Federal Courts, and that the Federal Circuit in *Schwendimann* had confirmed that this exceptional application of federal law to questions of ownership was confined to assignments of future, and not existing, patents. In his oral evidence Professor Thomas latterly seemed to accept that this body of law was not pertinent in this case and that the exceptional application of federal law to what Prof. Thomas was willing

to concede was a state law issue, namely construction of contracts, only applied to assignments of future rights:

> Counsel (BMS): [I]*f I can just refer you to what the Court in Schwendimann says. It refers to the Leland Stanford case as saying when the question is whether there's been an assignment of a future right or an agreement to assign a future right, that encompassing of that area into federal law does not apply for existing rights.*
>
> ...
>
> Prof. Thomas: *Again, this is a fairly narrow issue. This is when you have a contract, an actual assignment, a written assignment between two parties and there's a language of conveyance and one says "I hereby and do assign today", or "I shall assign and will assign in the future". Again, I agree that, generally, interpretation of contracts is a matter of state law. The Federal Circuit has said in this one situation we will federalise it so that we can have consistency about the language of conveyance. But then* Schwendimann *walks that back a little bit and says, well, that's only for future interests, it's not existing patents.*

[12] Professor Thomas cites two Federal Circuit cases in support of the proposition that an assignment is required before equitable ownership of patents can arise between members of a company group, namely *Spine Solutions* and *Abraxis*. Professor Thomas then cites six US District Court cases which he indicates build on the analysis of *Spine* and *Abraxis* (46 – 51 of first witness statement). The US District Court cases are: *Beam Laser*, *Steelcase*, *DePuy*, *Quantum Corp*, *Top Victory*, and *Digitech* – though only two of these cases post-date the Federal Circuit cases. A number of points might be made in this regard:

(i) Teva, through Prof. Thomas's evidence, relies purely on dicta of federal courts on ownership of patents, which the federal courts have explicitly and authoritatively stated is a matter of state law. Even if these judgments were authority for what is claimed (and as will be seen in point (ii), they are not) they could not and do not operate to affect the application of state law on the point in question;

(ii) as was outlined by Prof. Chisum the cases do not anyway support what is claimed for them (namely the setting down of a requirement of an assignment before an equitable interest can arise as between group companies). All of the cases are standing cases and in none of the cases referred to by Prof. Thomas does the federal court

override any state-law showing of equitable ownership;

[Thus, in his report, Prof. Chisum states as follows: 37 and 46.

> "*37. Paragraphs 41-44 of the Thomas Statement discuss the Federal Circuit's 2010 Spine Solutions decision. That decision noted that the only question in that case was whether a party was 'an exclusive licensee for purposes of standing.' The decision does not cite, discuss or repudiate any issue of state law. In passages Professor Thomas quotes, Spine noted that it was 'undisputed' that one entity was the 'sole owner,' that there was 'no agreement, either oral or written' with respect to a patent. The party asserted, at most, that there was an 'understanding' with the patent owner that it would have an exclusive right to practice the patent. That 'understanding' was not asserted to be one of ownership. It was 'at most' a bare license. Thus, Spine did not consider or reject any theory of equitable title based on the facts and the applicable state law.*
>
> ...
>
> *46. In paragraph 58 of the Thomas Statement, Professor Thomas asserts that I 'summarily' dismiss a 'long list of opinions 'holding that corporate parents do not hold equitable title in patents owned by their subsidiaries' because they 'primarily pertained to standing.' To the contrary, I carefully considered each case Professor Thomas cited and determined that they not only pertained to standing but also did not apply federal standing law to override a showing that a corporate entity had equitable title under state law. The decisions held that a corporate entity lacked standing because it did not possess legal title via a Section 261 assignment in writing. Some, such as* Beam Laser *(2000), and* Steelcase *(2004), ruled that a parent corporation failed to establish that it had 'equitable title' to patents to*

> *which a subsidiary held legal title such as would support standing to seek equitable remedies. In Beam Laser, the district court did not cite or consider any asserted provision of state law supporting such title. Had the parent done so, the district court would have been bound to apply that law, as the Federal Circuit confirmed in* Schwendimann *v.* Arkwright Advanced Coating*, 959 F.3d 1065 (Fed. Cir. 2020), discussed above. In Steelcase, the district court carefully considered the facts and found standing for one subsidiary but not another.*"

The following exchange also took place between counsel for BMS and Prof. Chisum during his re-examination:

Counsel: *It was put to you as well, Professor, if you have your report there again, it was put to you that you did not deal with* Beam Laser *in your report and the other US District Court cases. That was put to you by* [counsel for Teva]....

[Counsel then asked Prof. Chisum to read out the first six lines of the just-quoted §46 (down to the words "*state law*"). The following exchange then occurred]

Thank you, Professor. So what was your main point about your assessment of the cases that Prof. Thomas relied upon?

Prof. Chisum: *The point was that none of these cases say state law – if we had a case which said state law recognises equitable title to that patent in these circumstances, however we're going to disregard that.*

Counsel: *Yes.*

Prof. Chisum: *Based on federal law or policy. There's no case that says that, or even suggests that*.]

(iii) in the cases themselves no argument for an equitable interest as between group companies seems to have been made, possibly because most of the cases do not involve the company group itself arguing that one of their number should be allowed standing, but rather are cases in which a third party is bringing a declaratory action and seeking to join members of the group (*Top Victory* and *Digitech* v. *Newegg*) or in which a third party is suing on a patent that it has been assigned by a member of a group other than the legal title holder (*Abraxis* and *Quantum*).

[13] Footnote 3 in the *Digitech* case

Much reliance was placed by Prof. Thomas on footnote 3 in the *Digitech* case which states as follows:

> "*The only Federal Circuit cases that recognise an equitable title to a patent involve contractual arrangements to assign rights in inventions between the asserted equitable title holder and the inventor.…The Federal Circuit has also alluded to equitable title where the rights to a patent are being held in a trust".*

In his oral testimony, Prof. Chisum indicated that this footnote has to be read in the context of what the Federal Circuit was addressing, namely the circumstances in which standing will be accorded to a person who claims equitable title. In light of the well-established principle that state law governs ownership of property including intellectual property (which, as will be seen in the succeeding chapters, was also accepted by Mr Steele as well as Mr Chandler) and the explicit and repeated federal court authority on the specific point of state law governing ownership of patents, the conclusion to Professor Chisum's evidence regarding footnote 3 is most persuasive:

> "*So, that's basically what I read that footnote as being; you know, a contractual arrangement to assign rights and inventions between an equitable title owner and the inventor. That's the only type of case they have recognised. So, they are not saying, this footnote is not saying that; oh, the Federal Circuit would deny equitable title in any other situation, equitable title to the patent. That would be extraordinary. I don't really think Prof. Thomas was suggesting that. I hope he wasn't. He would say, oh, there can never be equitable title in a patent in a corporate situation. Ever? Whatever facts there are and whatever state law said? They're talking here, by saying only Federal Courts that recognise it, he means recognised it for standing purposes.*"

614. It seems safe to conclude from all of the foregoing that United States federal law is not engaged by the priority-related issue arising in this case, namely, whether one Delaware company, BMS Co, had the equitable ownership of the intellectual property (in particular, US165) of another Delaware company at a particular point in time.

615. In passing, I note that counsel for Teva complained in his closing oral submissions that at one point Professor Chisum referred to Professor Thomas as squirming on a particular point. Counsel for Teva suggested that for Professor Chisum to use the verb 'to squirm' "*was entirely inappropriate and again suggesting of advocacy*". But he seemed to me to have forgotten that when, in the course of cross-examination, counsel for Teva queried Prof. Chisum's use of this word, Prof.

Chisum immediately acknowledged that "*Maybe that was too colourful*" and indicated that he had merely meant that Prof. Thomas "*seemed to want to avoid*" a particular point (the applicability of state law). For my part, I thought this a trivial slip, almost to be expected in the course of sustained oral questioning, and not at all suggestive of advocacy: overall Professor Chisum gave balanced, respectful, and impressive testimony, and was an engaging and polite individual. I do not believe a man falls to be hanged for mis-speaking a single word, nor do I believe that Prof. Chisum's use of the verb 'to squirm' was suggestive of some wider deficiency in his evidence. In point of fact, no such wider deficiency presented.

VII. THE EVIDENCE AS TO DELAWARE LAW

19

The Evidence of Mr Steele

A. Introduction

616. Mr Steele is a former chief justice of Delaware and an expert on Delaware law. It was a privilege to have such a distinguished former member of the Delaware judiciary as a witness. Subject to para.4 of this judgment, an abridged version of Mr Steele's written evidence is set out at Appendix 12. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

617. In his initial statement, Mr Steele states as follows (at §2):

> "*I have been contacted by solicitors representing Norton (Waterford) Limited trading as Teva…to provide assistance on certain aspects of Delaware law in connection with proceedings in different jurisdictions in Europe. I have been informed that there are patent proceedings brought by Teva and its relevant entities within the Teva group against Bristol-Myers Squibb Holdings Ireland Unlimited Company…and its relevant entities within the…BMS group in relation to a patent covering the product, Apixaban, across various jurisdictions in Europe….I make this statement for the purposes of the Irish proceedings before the High Court*",

and observes as follows (at §21):

> "*I have reviewed the Holland report and have been asked to provide my observations and comments on two general topics addressed in that report.*"

618. An account of the evidence that Mr Steele gave when examined, cross-examined, and re-examined follows hereafter.

B. Examination

1. Corporate Separateness

619. Asked by counsel for Teva about the principle of corporate separateness as a matter of Delaware law, Mr Steele observed as follows:

> "*One of the fundamental bulwarks of Delaware corporate law is a recognition that there's separation between the parent corporation and any subsidiaries or affiliates. That is a very attractive prospect for both corporations, because they like to place assets in subsidiaries to get the kind of separation from potential liability and taxes that can occur when you have that doctrine of separateness. And there's a legion of cases that restate that time and again. Secondarily, but important to that is the recognition in Delaware case law, that even if the parent is a 100% stockholder of the subsidiary and the subsidiary does have assets, the parent is not the owner of those assets until a time of dissolution under Section 271.*"

2. Exceptions to Corporate Separateness

620. Asked by counsel for Teva whether there are any exceptions to the principle of corporate separateness, the following exchange occurred between Mr Steele and counsel for Teva:

Mr Steele: *There are actually three. I only address two in my report, because only two are relevant. The first is …§ 220 of the Delaware general corporation law, which provides for access to books and records of the corporation. The second is an appraisal statute recently amended that allows participation and appraisal beyond what we had in the past, but that's not relevant to anything we're talking about today. And the last is Section 271, which addresses the issue of at the time of sale of all or substantially all of the assets, the parent can consider the subsidiary to be part of its assets at that time. But the statute very carefully says for that purpose only.*

Counsel: *....And I think the third, which you don't deal with but exists and there's no dispute about it, is veil piercing, is that correct?*

Mr Steele: *I didn't address that, because the facts didn't suggest to me that that was an issue before the Court.*

3. What Happened Here

621. Noting that following the acquisition of the Dupont Company, there was a change in name and the application was left in the subsidiary, with an assignment from the inventors to the subsidiary with matters being left as they were until 2007, counsel for Teva asked what significance Mr Steele attached to how things were done. In response, Mr Steele indicated as follows:

> "*The reasonable inferences to draw from what happened, at least in my view and what I think would be drawn by our courts, when the business, the parent business, makes a decision to place assets in a subsidiary that's a conscious desire to free themselves from potential taxation and potential litigation which might result in money damages. That's particularly important at the conclusion of an acquisition, whether it's asset acquisition or whether it's an M&A agreement….Despite the reps and warranties that might be in those agreements, there's always care to make sure that the purchaser can be insulated from liability that they take on when they make that purchase. So, it seemed perfectly reasonable to me, when I reviewed the facts for BMS to make that decision to segregate those patents, leave them where they were and wait for a period of time. Whether they had the statutes of limitations in mind or not, I don't know, but it's a very common experience for them to do so and it's one of the attractive features of corporate separateness.*"

4. Assignment of 2007

622. Asked by counsel for Teva where he saw ownership of the patent to lie before the assignment of 2007, Mr Steele indicated that "*There was no, to my knowledge, shift of title prior to that assignment*".

5. Beneficial and Legal Title (*Hologic*)

623. Asked by counsel for Teva whether he saw anything to suggest that there was a separate beneficial and legal title preventing *vis-à-vis* the ownership of the patent, Mr Steele responded as follows:

[(i) What is Meant by Equitable Title]

> *"Separate beneficial and legal title is confusing in the case law. What I understand this phraseology of equitable title to mean tends to shift from case to case. And let me suggest to the Court that perhaps Hologic is a case that illustrates that better than any other. In the beginning of that opinion, Judge Robinson says that her holding is that the party has equitable standing and then she, like some of the other cases, refers to it*

as equitable title. My understanding is, without a transfer or assignment under federal statutes, that there is an equitable financial interest in the patent on the part of a parent that would not be titled by law as the owner. And that asset and that beneficial interest can be protected by the parent through equity, an equitable claim or seeking an equitable remedy…. So, in my view, the correct way to illustrate this concept is to refer to it as an equitable interest, a financial interest in the future of the patent which gives you a limited opportunity or right to seek equitable relief if that interest is endangered by a third party."

[(ii) Conflation of Equitable and Legal Title]

"The problem with some of the language in this case that I've seen and some inferences that have been drawn is there's an attempt to conflate equitable title with legal title. And I think, given the fact that legal title is so critically important to the public generally to know on a given day at a given time who carries all the legal rights of ownership to that patent, that to be imprecise when you make references to that segregation of equitable remedies from legal title will confuse the public. Why have a registry system at all if one can't rely on it, that one doesn't know, despite the fact the patent is registered to Pharma as the titled legal owner that lurking in the shadows somewhere is this inchoate interest that may spring out in a cert, for priority or otherwise, that it in fact is tantamount to legal title. That, as I mentioned earlier about Delaware's focus being on clarity and consistency and confidence in the outcome, that creates an uncertainty and lack of predictability that would be contrary to Delaware law."

6. Distinction Between Federal Law and Delaware Law?

624. Asked by counsel for Teva whether he perceived there to be any difference between the doctrine of corporate separateness as it presents in Delaware law and under Federal law, Mr Steele indicated that "*the Federal cases seem to state it's the same*".

7. Subsidiary Bankruptcy/ Liquidation

625. Asked by counsel for Teva "*in terms of a subsidiary, if a wholly owned subsidiary goes into, I think you have bankruptcy or we would call it liquidation, who gets access to the assets of the subsidiary*", Mr Steele indicated that the creditors do.

8. The Emails of October 2001

626. Asked by counsel for Teva whether there is anything in the exchange of emails of October 2001 that suggests there was an assignment of any interest in this patent to BMS Company, Mr Steele responded as follows:

"*No. In fact what it did for me when I read it was confirm that the business interests were satisfied by taking the step of purposely leaving the patent Pharma and not transferring it to BMS and making the express distinction between what other products that might produce or work that might produce patents through the DuPont acquisition, those new patents would be assigned to BMS. That reinforced, in my mind, the desire for that separation that was important to the company at the time.*"

9. The CME Case

627. Brought by counsel for Teva to the *CME* case and the reference therein that:

"[A]*n interpretation that does not include a parent corporation's interest in its wholly owned subsidiary's assets or a corporation's interest in its affiliate corporation's assets. Class Counsel rest their interpretation of 'beneficial ownership' on two passages in Fletcher's Cyclopedia...*",

and asked to give his view as to the relevance of his passage to Delaware state law, Mr Steele responded as follows:

"[T]*his reference...really complies with the fundamental doctrine of corporate separateness. In this situation, when seeking to address their share as they saw it of the funds of the settlement, a parent and a subsidiary tried to combine their resources to present themselves to the Court as a team that had qualified to participate in the settlement. The Court rejected that on the theory that, basically, you chose to be separate entities, you have to live with that now…*[I]*t's consistent with Delaware law that if you select this corporate form, the Court's understanding is that you did it for a proper purpose, that it serves your needs at the time and you would have to alter that structure just because it might be disadvantageous to you down the road to have made that selection.*"

628. Asked by counsel for Teva to comment on the relevance of the just-mentioned proposition to the present case "*in terms of the placing of the patent in the subsidiary as opposed to BMS*", Mr Steele observed as follows:

"*In my view, it's directly relevant, because it substantiates the fact that at the time… the patent in issue was placed in Pharma, there was a conscious business decision made to segregate it and there were good sound reasons for doing so, as I explained earlier, I think. And it can't be a matter of convenience; on Monday you have it there, on Tuesday some inchoate kind of interest allows you to act differently. You're stuck with it until you take the step that BMS actually did take and that was six years later, to transfer the patent consistent with federal law.*"

629. Asked by counsel for Teva what he meant by the term "*inchoate right*", Mr Steele observed as follows:

"*What I mean by that is, as the federal cases suggest, when the facts justify it, that there is an equitable interest, an equitable standing, as I think Judge Robinson put it best, … that equity that applies and the opportunity for equitable relief is something very distinct from legal ownership.*"

630. At this point, Mr Steele returned to his point regarding conflation observing as follows:

"*It's not really ownership, it's a right of standing to bring an action. And that, I think, is what somehow gets conflated when you're not taking that action, even though it's available to you, because the circumstances don't call for that claim or remedy, yet you want to claim that it's as if you had that right before or legal title. You can't conflate legal title in the equitable interest that gives you standing to bring a suit in equity. That's my point.*"

10. Beneficial Ownership of Subsidiary Assets

631. Asked by counsel for Teva whether there is any basis in Delaware law for a parent subsidiary enjoying beneficial ownership of some assets and not others, the following exchange occurred between Mr Steele and counsel for Teva:

Mr Steele:	*Beneficial ownership in what? The asset?*
Counsel:	*Sorry, of some of a subsidiary's assets and not others.*
Mr Steele:	*No. Delaware law is clear; on dissolution, the parent owns the assets, but not before that.*
Counsel:	*And that's on dissolution where, I take it that there is a solvent dissolution, is that correct?*
Mr Steele:	*Well, 271, sale of substantially all or all of the assets. The subs are considered to be the same as the parents at that point.*
Counsel:	*And I think the wording of Section 271 specifically provides that it's only in those circumstances that the parent has the right to sell the subsidiary's assets, is that correct?*
Mr Steele:	*That was the most recent amendment to make that very clear, that the subsidiaries, which used to be included by thought at that point, now expressly are part of the 271 sale of all or substantially all of the assets. But that statute limits that kind of, for lack of a better term, exception to corporate separateness for this purpose only.*

11. *Hollinger*

632. After counsel for Teva touched on the *Hollinger* case, Mr Steele offered the following view:

> "[B]*oth former Justice Holland and former Chancellor Chandler are saying...that Hollinger somehow stands for the proposition that the exceptions to corporate separateness can be in pragmatic situations expanded beyond 220, the Appraisal Statute, and 271. However, that's not what the opinion says. The opinion discusses that there may be pragmatic circumstances that ought to be considered by the Court on a case by case basis going forward, where corporate separateness might be ignored…. Vice Chancellor Strahan at the time concluded…. that while his … musings and dicta, might be a good place for the law to go, he didn't have time to either say it should, it has, it ought to. And he moved on to the real holding of the case, which was simply that he didn't have to address that, because under 271, his very careful and thoughtful economic analysis of the value of The Daily Telegraph and The Spectator relative to the other assets that Hollinger International owned did not constitute all or substantially all of the assets. Therefore, no vote by the parent's stockholders was required under Section 271. That's the holding of the case. It was appealed almost immediately. And I was on the Supreme Court when it came to us on appeal. It was affirmed on the basis of that holding and no other basis.*"

12. Parental Right of Innovation and Beneficial Interest

633. Brought by counsel for Teva to the section of his opinion where he states as follows: "*The mere possibility for a corporate parent to instruct a subsidiary to assign an asset does not, under the laws of Delaware, equate to an assignment actually carried out*", and invited to elaborate on this observation, Mr Steele indicated as follows:

> "*This was a placement of a patent, as I view it, for the convenience of the parent and when it was no longer convenient to the parent, the parent completely complied with the assignment process contemplated by federal law. That was six years later. In between what those consequences may be under federal law is beyond my purview. But there was no contractual obligation at all until the parent changed its mind and said it's no longer efficacious for us to keep the patent in Pharma, so we're going to have it assigned to us.*"

C. Cross-Examination

1. Economic Interest

634. Asked where he referred to 'economic interest' in his report, Mr Steele indicated that he had not used this particular term. Touching later on the issue of economic interest, Mr Steele confirmed a view he had expressed in the Finnish limb of these proceedings, that view being:

> "...[I]*n several cases, there's loose language...referring to equitable title...*[A]*ll the reports of the experts, I think, identify, where that issue is addressed in the federal district courts, sometimes...*[as] *equitable interest, sometimes...equitable title, but the...only advantage that the beneficial owner has by equitable alleged title is the ability to seek relief if that economic interest is harmed by another party through an equitable claim or an equitable remedy….*[E]*quitable interest in a patent means that that particular interested owner, in the event someone attempts to or damages that economic interest, the equitable interest or owner can bring an action to enjoin and stop that harm, because injunctive relief is a relief in equity...*[T]*hat's distinguished from the right of the legally titled owner of the patent, to sue the infringer of that patent*".

2. Beneficial Interest

635. Asked to confirm what he had said to the Finnish court in parallel proceedings brought in that jurisdiction, the following exchange occurred between counsel for BMS and Mr Steele:

Counsel:	[D]*id you say on a number of separate occasions to the Court in Finland that BMS Co enjoyed beneficial interest in the patent that we're all discussing in this case?*
Mr Steele:	*I did.*
Counsel:	*And I take it…you were acknowledging that as an ownership interest in the patent, though you did distinguish it from legal interest, isn't that right?*
Mr Steele:	*In part. But actually… Judge Robinson's case provides, it's an interest economically that allows, under the context of this case, the parent who doesn't have legal title to the patent to protect its economic rights through equity….So, it's equitable standing.*
Counsel:	*But sorry, Mr. Steele, just to be clear, when you talk about economic rights, you're talking about rights you have as a consequence of beneficial ownership, isn't that correct?*
Mr Steele:	...[Y]*es.*
Counsel:	*...So, insofar as your evidence is concerned, you accept that BMS Co had beneficial ownership and, therefore, had standing to seek equitable remedies to protect the patent, is that correct?*
Mr Steele:	*To protect its economic interest in the patent, yes*.

3. Delaware law and Federal Law

636. In response to a question from counsel as to whether his view as to how Delaware law relates to federal law remains the same as when he gave testimony in Sweden, Mr Steele indicated that it does, that view being:

> "*Delaware law determines ownership of a patent or the rights to a patent and federal law develops a process for effectuating the patent itself, and for protections of the patent by a system for getting protection for others who interfere with the patent. The*

only issue for the States and Delaware is who owns in the sense or who is the legal owner and who, if anyone, is the equitable or hasn't equitable interest in the patent."

637. I will return to this quote later below as it is of some significance in terms of how this case falls rightly to be adjudicated.

4. Crux of Differences between Mr Steele and Mr Chandler

638. Asked about the crux of the differences between himself and Mr Chandler (and the late Mr Holland), Mr Steele affirmed the view that he expressed in Sweden, that being:

"*I think the crux of the differences… is on the language…BMS had unfettered and absolute rights to the patents owned by its wholly owned subsidiary, BMS Pharma…. I think the way to address that issue of the nature of the ownership of the patents is that BMS Pharma had legal title and the word title has significant meaning to the patents. The parent BMS had an equitable interest in the property, but not an equitable title*,"

adding

"[T]*o use the word title conflates the significance of the nature of their interest*",

and later continuing as follows,

"[T]*itle suggest*[s]*, I think in both common law and the statutory law in Delaware means a formal process for initially obtaining title in the public forum, which is noticed to all in the public, that this is the owner with the legal rights as well as equitable rights to that property. A better way to look at the distinction between the discussions and the reports about equitable ownership and legal title is to focus on the word ownership, rather than rights or title…. So, the real problem that I have with the other opinions is the absolute nature of them in suggesting that the parent had an unfettered or absolute right to the ownership of the patents*".

5. Regulation of Assignment of Patents

639. Mr Steele confirmed that the view he expressed in Finland regarding the assignment of patents remains the same, that view being as follows:

"*The assignment process of a patent is subject of federal law. Now, my expertise does not extend to the niceties of the federal process system, but the one issue that I believe I and the other experts agree upon is the fact that the issue of ownership of a patent is a matter of state law….The reason or rationale for that is because like contract law, ownership of assets is a matter of common law, or statutory law within the states, and not within the purview of the federal government.*"

640. I note that when it comes to federal law versus state law, a key element of Prof. Chisum's evidence was that state law governs ownership. (Federal law, I note, also only applies by virtue of a specific provision.) Neither proposition takes from the fact that there is federal provision (constitutional and statutory) concerning patents. Thus, the US Patents Act is clearly and undeniably an instrument of federal law. However, this case, where the issue is whether BMS Co., a Delaware company, has equitable ownership over the property of another Delaware company, is a question of state law and there is no specific federal law provision that applies; in particular, no provision of the Patents Act is relevant to that question. Notably, the evidence of Mr. Steele, the expert witness called by Teva, is consistent with the evidence of Prof. Chisum.

641. In the above quote, Mr Steele is separating contract law from ownership of assets. Whereas Prof. Thomas in his evidence was willing to concede that state law applies to interpretation of contracts, but not generally to ownership (at least as I understand his evidence), here, Mr Steele clearly states that "[L]*ike contract law, ownership of assets is a matter of common law, or statutory law within the states, and not within the purview of the federal government*".

642. I have also quoted previously above the following answer to a question posed by counsel for BMS to Mr Steele:

"*3. Delaware law and Federal Law....*

In response to a question from counsel as to whether his view as to how Delaware law relates to federal law remains the same, Mr Steele indicated that it does, that view being:

'Delaware law determines ownership of a patent or the rights to a patent and federal law develops a process for effectuating the patent itself, and for protections of the patent by a system for getting protection for others who interfere with the patent. The only issue for the States and Delaware is who owns in the sense or who is the legal owner and who, if anyone, is the equitable or hasn't equitable interest in the patent.'"

643. So, there is clearly agreement between Prof. Chisum (called by BMS) and Mr Steele (called by Teva) in relation to the fundamental proposition that ownership of patents is a matter for state law.

6. Seeking Legal/Equitable Relief

644. Mr Steele confirmed by reference to certain of his observations in the Finnish proceedings that it is his view that if one holds both the legal and beneficial interest or ownership in a patent one can seek legal and equitable relief; however, if one holds beneficial ownership only one is confined to seeking equitable relief.

7. Beneficial Interest and Priority

645. Asked whether a beneficial interest (of the type that BMS Company claims in these proceedings to have enjoyed in the assets of BMS Pharma) would have given it the right to claim priority from the priority application, Mr Steele affirmed the view that he had expressed in the parallel Finnish proceedings, that view being as follows:

"*Now, I have to give you this caveat, I don't claim to be an expert in patent law, and what the federal system would say about priority under those circumstances is outside my expertise. I can only say that the matter of ownership of the patent did not at that point convey to BMS legal title. If legal title's what's required for priority under the federal system, maybe so, I expect the other experts would answer that question, I can only say that the only ownership interest, which is determined by state law, that BMS had was this equitable interest and ability through equity in... by claim, in equity by remedy to protect that economic interest, but it does not, and should not be conflated with legal title, whatever that means in the federal patent system.*"

8. Beneficial Owner, Legal Owner and Public Registers

646. Asked whether, as a matter of Delaware law, he would cavil or argue with the proposition that the beneficial owner is regarded as the real owner, though it may not have the title, Mr Steele responded as follows:

> "*In a situation where there's a public registry like a patent, I would have difficulty concluding that until you put the public on notice that you now have both the beneficial and the legal rights as complete, for lack of a better term, owner of the patent…*[Y]*ou do the public a disservice if you're playing a shell game on who has what rights on any given day. What's the point of a registry?... In developing these relationships, one has to take into consideration, particularly in equity, the effect on the public and public policy. Public policy is to register the title legal ownership so the public knows who to go to for a licence, who to expect to be able to transfer the patent to them. You can't have this kind of inchoate relationship. That's the kind of confusion and uncertainty that Delaware law won't tolerate.*"

647. Asked whether he accepted "*that the courts of Delaware have, without difficulty, found in respect of, for example, real property in the name of one person, that the real or beneficial owner is somebody else*", Mr Steele indicated that this was so "*but that's not within the context of corporate separateness*".

648. Asked whether there are not abundant "*decisions of the Delaware Courts of Chancery, where the fact that something is registered even in a public register in the name of one person doesn't stop the Court finding that some other person, not the legal or titled owner on the register, is the real owner*", Mr Steele agreed that this was so.

9. Interactions Between the Parent and the Subsidiary

649. Counsel for BMS referred back to a question and answer exchange that had arisen between counsel for Teva and Mr Steele during the examination in chief, that exchange being as follows:

> Counsel (Teva): *So, one more question on this topic. If we have a case at hand that we have a parent and a subsidiary, and the parent owns hundred per cent of the subsidiary, can the subsidiary company, which has under its own name patents, and trademarks, and so forth, under the Delaware state law do whatever it wants with those assets, whether they are patents or trademarks, so can they do whatever they desire with them without being feared of any consequences if ever the parent company disagrees with these acts they've been doing.*
>
> Mr Steele: *They cannot, and as all three, I think, of the expert reports relating to Delaware law make clear, the subsidiary owes fiduciary duties of loyalty and care to the parent. So, they can't...even though they are the legally titled owner of the patent, they can't act in their own interest…*[if] *contrary to the parent's, or in anyone else's interest that would be contrary to the parent's.*

650. Arising from this earlier exchange, the following exchange occurred between counsel for BMS and Mr Steele

> Counsel (BMS): [T]*he point I just want to put to you about this, insofar as Delaware law is concerned with a wholly owned subsidiary, like here Pharma, you have accepted that BMS Co owns the beneficial interest in the patent in question, you have accepted because of corporate control there would be no difficulty issuing an*

instruction or direction to the subsidiary. And your evidence and your acceptance now is that in fact the subsidiary could do nothing with the patent, or indeed any asset, contrary to an instruction of the interests of the parent, isn't that correct?

Mr Steele: *Well, contrary to the best interests of the parent, yes. And as a pragmatic point of view, I try to point out that's not a legal rule. They would do what the parent requested them to do, because it's assumed that they will act in the best interests of the parent. And the parent knows what its best interests would be.*"

10. Nature of Alleged Gap in Ownership

651. Asked by counsel for BMS what portion of ownership, other than legal interest, BMS Co. did *not* have before an assignment occurred, the following exchange transpired between Mr Steele and counsel:

Mr Steele: *Well, they had the rights only that accrue to a beneficial owner through equity, as I've described.*

Counsel: *....So there was nothing else then? You had the beneficial ownership with the rights flowing from that. What you didn't have, on your testimony, is the registered legal interest and the rights that flowed from that, isn't that correct?*

Mr Steele: *...I tend to view it more that it wasn't a question of was there anything else. My interpretation of the law is that was all they had. Whether there's something else out there that flows from legal title beyond what's described in the federal law, no, there isn't anything else. But that's all they had. They didn't have legal title….*

Counsel: *Well, that's the only thing they didn't have, Mr. Steele, can we agree on that?*

Mr Steele: *Yes, I agree on that.*

11. *Hologic*

652. Counsel for BMS brought Mr Steele to the observation of Robinson J. in *Hologic* that "[T]*he issue of standing is rooted in the facts of each case…*[and]*…the record at bar is sufficient to demonstrate that 'boundaries between the corporations* [at bar] *have been breached'*", counsel then putting it to Mr Steele that:

> "*Chancellor Chandler will tell the Court that as far as he is concerned, the exercise engaged by Judge Robinson here in this case is precisely the exercise that would be engaged by a Delaware Court of Chancery and that in all material respects, the position in this case is materially the same and, therefore, in this case all necessary ownership interests to treat BMS Co as the real owner were vested in BMS Co. Do you agree or disagree with that* [view]?"

653. To this Mr Steele indicated as follows:

> "*I don't agree with it, for the reasons I said before. I think the interest that's transferred under those circumstances is standing to seek equitable relief because you are a beneficiary owner. It can't be conflated into all of the consequences of legal title.*"

654. At a later stage in the cross- examination, counsel for BMS and Mr Steele returned to *Hologic* again in the following exchange:

Counsel:	*You having accepted that the beneficial ownership of this patent rests with BMS co, and* Hologic *found that because of the nature and extent to which the asset of the subsidiary was being managed by the parent, that in those circumstances, the boundaries had been breached, as Judge Robinson put it….*
Mr Steele:	*It is correct that she put it that way. But more importantly to me, she found that the consequence of that, and her holding was that ownership concept only gave standing to bring actions to protect that interest in equity, and particular injunctive relief from harm that was being done by a third party. She made her holding based upon equitable standing.*
Counsel:	*Where… does Judge Robinson draw the distinction you have now just drawn? ….*
Mr Steele:	[W]*hen she states what her holding is, she states that she finds equitable standing which gives the opportunity for equitable remedy and to seek equitable relief generally, no more than that.*
Counsel:	… [S]*he couldn't have made that finding unless she had already found that the beneficial owner of the patents in question was the parent. Isn't that correct?*
Mr Steele:	*It's correct that she found there was a beneficial ownership that gave rise to the standing, yes….But there's a considerable difference between legal title and the economic interests that gives rise to standing to seek equitable relief if your economic interest is being endangered…*
Counsel:	[E]*xpressly, Judge Robinson found in Hologic one of the bases for her finding was because of the nature of the control the parent exercised over the subsidiary's patents, isn't that right? …*
Mr Steele:	[T]*hat's the way she phrased it, yes.*

12. *Shaev*

655. Counsel for BMS brought Mr Steele to the decision in *Shaev*, which, he posited is an example of "*the Court not allowing the strict terms of a statutory provision to create an unfairness or prevent equitable concepts operating*". Mr Steele agreed that this was so.

13. Operation of Equity in the Presence of Statute

656. From the written reports of Messrs Steele and Chandler, there was a perceived difference between them concerning the operation of equity in the presence of statute. In fact, Mr Steele made clear that his view of the operation of equity in this context accords with that of Mr Chandler, being as follows:

> "*There are circumstances under which equity can intervene not to change a statute or the policy behind it, but to prevent its application under circumstances …. after weighing the harm would way too heavily against one party and not heavily enough in favour of the other party. That's part of equity's intervention in Delaware*."

14. *Lynch*

657. Brought by counsel for BMS to the decision in *Lynch*, Mr Steele indicated that he was not familiar with the case or prepared to comment on excerpts from it, though he noted that: "*I see references to sham documents and fraudulent inducement. If those are the circumstances, I would not be surprised that equity would step in.*"

15. *Cartanza* and *Taylor*

658. Counsel for BMS brought Mr Steele to the decisions in *Cartanza* and *Taylor* as further examples of:

> "*the Court of Equity…not* [being] *constrained by corporate separateness by contracts, by public registers, be they for licence plates or for shareholdings or for real property. Whoever the party is who's registered with legal title, the Court, at all times, will deploy its analysis to determine whether or not the beneficial or real owner is somebody other than the registered owner, isn't that correct?*"

659. To this, Mr Steele responded as follows:

> "*No, I don't think so. I think the fundamental value of corporate separateness is too important to the State of Delaware for there to be anything other than a reading of 271 that the assets are not owned by the parent or controlled by the parent except when they're being disposed of by a sale of all or substantially all of the assets. All these other situations are not controlled by corporate separateness, they're all different circumstances where equity can intervene in order to get a fair result. This was a conscious business decision to place the patent in a subsidiary and title that subsidiary as the owner, the legal owner, of the patent. It's not lightly dealt with that once you make that decision, you can then just, in an inchoate kind of ownership, have it both ways; on Monday when you want legal title, you can claim all the benefits of legal title because you have beneficial ownership; on Thursday you go back to no, I'm not responsible for any of the debts, any of the liability addressed to that patent, because it's in the hands of the subsidiary, I don't have to pay taxes on any revenues from that patent because I'm the parent, I'm not the owner. You simply cannot have it both ways. And that's something equity's going to consider. While I take all your points about there are circumstances where beneficial ownership has significant meaning in the context of that particular fact situation…it really boils down to the importance of corporate separateness at the end of the day in the corporate world.*"

16. Section 271

660. Turning to the precise ambit of §271 the following exchange occurred between counsel for BMS and Mr Steele:

Counsel:	*Just to be clear… the Court of Equity is empowered to make a finding in all sorts of circumstances, including where there's corporate separateness as to who the beneficial owner is and whether that entity or person is different to the legal owner..?*
Mr Steele:	*I agree with that.*
Counsel:	*And in those circumstances, Section 271 can have no impact on the jurisdiction of the Court of Chancery to exercise that function?*
Mr Steele:	*271 applies only in the context of the relationship between a parent and a subsidiary….*
Counsel:	[N]*o statutory amendment was made to prevent the Courts of Equity engaging in the substantive exercise of review to identify who a beneficial owner was..*?
Mr Steele:	...[T]hat's correct.

17. *CME Group*

661. Counsel for BMS brought Mr Steele to the *CME Group* case and, amongst other matters said:

> "*The point I'm simply putting to you is Section 220, like Section 271, like Section 225, are providing statutory rights, but the provision of those rights does not impact the jurisdiction of the Court of Equity to identify who the beneficial owner is.*"

662. Mr Steele agreed with this proposition.

18. Disagreement with Judge Holland

663. Counsel for BMS brought Mr Steele to the section in his report where Mr Steele states as follows:

> "*I disagree with the following two opinions that Justice Holland offered in his report: First, he opined that 'as a matter of Delaware law, when BMS filed the later patent application in 2002, by virtue of its 100% ownership of its subsidiary Bristol Myers Squibb Pharma Company, and its stated internal policy as to patent filings, BMS had the unfettered right to call for such subsidiary to assign to BMS the right to claim priority from the earlier filed patent application.*'"

664. When it was put to Mr Steele that he had indicated in his evidence in Finland that he did not actually disagree with the just-quoted proposition but rather disagreed with the proposition '*that that calling would effectuate the legal transfer*' Mr Steele agreed that this was so .

665. A second point of disagreement with Judge Holland, as stated by Mr Steele in his report is the following:

> "*Second, he* [Judge Holland] *opined that 'BMS had and has the absolute right to direct the legal title holder of the patent, Bristol Myers Squibb Pharma Company, to take any and all action regarding the patent that is in the best interest of BMS.*'"

666. Having read this text aloud, counsel for BMS then put the following proposition to Mr Steele

> "[A]*gain if I understand your evidence from Finland, and the exchange we've been having this afternoon, you actually don't disagree with that proposition either…. I understand the distinction you …. draw…*[is] *to the vesting immediately of the legal title?*"

667. Mr Steele agreed that this was so.

668. Next, counsel referred Mr Steele to the following observation in his opinion: "*Further, the mere possibility for a corporate parent to instruct a subsidiary to assign an asset does not, under the laws of Delaware, equate to an assignment actually carried out,*" and then put the following question to Mr Steele:

> "[T]*hat, again, is a reference to the legal or registered interest, if I understand your evidence, not the fact that the beneficial interest was in BMS Co, isn't that… correct?*"

669. To this Mr Steele responded that "*It doesn't go to whether there was beneficial ownership, it goes to the fact that it wasn't effectuated.*"

D. Re-Examination

1. The Decision in *Hawk* (Asset Partitioning)

670. Counsel for Teva drew the attention of Mr Steele to the observation in *Hawk* that:

> "*The Memorandum Opinion did not engage in veil piercing. As this court has explained at length elsewhere, the separate legal existence of juridical entities is fundamental to Delaware law, as are the correlative principles of limited liability and asset partitioning...*"

671. The following exchange then occurred between counsel for Teva and Mr Steele:

Counsel:	[A]*sset partitioning is a correlative principle of corporate separateness, is that correct?*
Mr Steele:	*That's correct.*
Counsel:	[W]*hat is meant by 'asset partitioning'?*
Mr Steele:	*You partition the assets when the parent decides what assets it will retain, if any, and place what it wishes in a subsidiary.*
Counsel:	*And when those assets go into the subsidiary, what is the ... legal consequence of that?*
Mr Steele:	*Even if the parent owns a 100% of the shares or is a controller, those assets belong to the subsidiary, not to the parent.*
Counsel:	*You say that the parent can have a right to call for assets…is that correct?*
Mr Steele:	*I'm saying that it's highly unlikely, as a practical matter, if the parent called for an asset to be transferred that the subsidiary, given its fiduciary duty, would not agree*.

2. A Parent Company 'Shell Game'

672. Counsel for Teva noted that Mr Steele had referred under cross-examination to a parent company playing a 'shell game' and asked what he meant by this. To this, Mr Steele responded as follows:

> "*What I meant to* [do was to] *characterise perhaps in too casual a way, the essence the quote the Court heard earlier from Fletcher's Cyclopedia and that is from the CME case, that you can't have it both ways. If you decide to put assets in your subsidiary, you have to live with that, and the consequences of that, because you get benefits from that. And it's a balancing that it's assumed that the parent has made as a good business decision. And you can't bait and switch in that respect. If there's a transfer process that will get the asset back in legal title with the parent, that can be effectuated. But until it is, the asset's still owned by the sub.*"

3. *Maquet*

673. Counsel for Teva referred Mr Steele to the decision in *Maquet* where the following is stated:

> "*The Court is wary of extending the doctrine of equitable title to situations where a corporate parent exercises control over a patentee subsidiary. Generally, remedies in equity are created in order to avoid unfair results. There is nothing unfair about a corporate subsidiary owning title to a patent, or a corporate parent exercising substantial control over its subsidiary. Furthermore, it is not clear how far such an equitable right would extend and how it would be exercised - surely not every corporate parent has an equitable title to patents held by every corporate subsidiary.*

Perhaps most importantly, extending the doctrine in such circumstances directly contradicts the statutory requirement that assignment of patent rights must be by an 'instrument in writing'."

674. Asked to comment on this observation, Mr Steele responded as follows:

"*I think, and what I have opined, is that the beneficial ownership concept goes only so far as to give the parent who doesn't have legal title the opportunity to exercise its rights to protect its financial interest by way of equitable claims and equitable remedies. And I think this is a caution to be careful extending that.*"

4. *Hologic*

675. Counsel for Teva noted that Mr Steele had stressed that *Hologic* had established an equitable standing to pursue injunctive relief. Mr Steele indicated that his was so.

5. Resulting Trusts

676. Counsel for Teva queried the relevance of the concept of resulting trusts to the case at hand (as posited by BMS). Mr Steele indicated that to his mind this concept is not relevant to the case at hand.

6. *Shaev*

677. Brought by counsel for Teva to the decision in *Shaev*, Mr Steele indicated as follows:

"[That case involved] *an interpretation of the policy behind the statute*....[a]*nd that policy was pretty narrow. That policy was intended to prevent someone from buying an interest in litigation, by buying stock after they knew there had been a breach of fiduciary duty, they didn't own the stock at the time, therefore they wouldn't have standing under Delaware law to bring the action. But because of this situation, where a shareholder owns stock in both a parent and a sub and the parent divested itself of the sub and after that the circumstances of the development of that deal constituted a breach of fiduciary duty in the mind of the plaintiff. And the plaintiff didn't sue* in a double derivative way*, but then sued because of the share that it had gotten after the wrong had happened in the sub. And the conclusion I reached was the purpose of the statute was to prevent barratry, it wasn't to go through some convoluted process where suddenly, without any control over the situation, the stockholder lost standing. So, as a matter of equity, it allowed that stockholder to have standing,* [*i.e.*, statute did not prevent standing in that instance]."

7. Section 220

678. Counsel for Teva brought Mr Steele to the *Hollinger* case and enquired about the inclusion of the word "*only*" in §221 following on that case. To this, Mr Steele responded as follows:

"*My assumption has been… because of the musings …questioning the scope of exceptions to the general rule that were suggested in dicta in Hollinger that the General Assembly wanted to make sure it went no farther and say that that exception only exists under circumstances where the parent is selling itself, or itself and the sub or substantially all of the assets, all or substantially all of the assets, which would cabin or curb too much interventionist work by chancery going forward.*"

8. The BMS Manual

679. Counsel for Teva brought Mr Steele to the observations in the BMS manual (p.84 of manual; p 171 of booklet of *viva voce* examination of Scott Brown) indicating which patents to put in a subsidiary and which to put in the parent company, noting that this was consistent with Mr Steele's previous evidence about "*making a deliberate decision as to where to place a patent*" . Responding, Mr Steele observed as follows:

> "*That* [*i.e.* making a deliberate decision as to where to place a patent] *was very important to my consideration, whether there was a good business reason for placing it in the sub. And this reaffirmed to me that that was the intent, to have the legal title to the patent in the sub. And if the situation would change, they'd change it later, which they did, six years later.*"

9. Economic Value

680. Brought again to the notion of 'economic value', to which he had made reference in his earlier evidence, and asked what he meant by "*having a right to claim equitable relief to protect that economic value*", Mr Steele indicated as follows:

> "*I mean exactly what Judge Robinson said; that is that you would be able to have equitable standing to bring an action in equity to protect your interest in seeking an equitable remedy to stop damage to your asset.*"

20

The Evidence of Mr Chandler

A. Introduction

681. Mr Chandler is a former chancellor of the courts of Delaware and an expert on Delaware law. He was the youngest person appointed to the Delaware Supreme Court in 1986 and in 2009 became the longest-serving justice in Delaware history. It was a privilege to have such a distinguished former member of the Delaware judiciary as a witness. Subject to para.4 of this judgment, an abridged version of Mr Chandler's written evidence is set out at Appendix 1. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

682. In his initial statement, Mr Chandler describes his role in the following terms:

> "*McCann FitzGerald LLP sought my expert opinion on the questions that had been presented to Justice Holland, taking into account the matters stated in the Golian Statement and disregarding the content of the Mathias Statement, i.e., whether, as a matter of Delaware law, when...BMS Co...filed the later patent application in 2002, by virtue of its 100% ownership of its subsidiary...BMS Pharma...and the matters set forth in the Golian Statement, BMS Co: (i) had the unfettered right to call for such wholly-owned subsidiary to assign to BMS Co the right to claim priority from the earlier filed patent application; and (ii) could be characterized as the beneficial owner of the earlier filed patent application. To the extent I was not familiar with the case law referenced in the Holland Expert Report, I have reviewed the relevant cases*.".

683. An account of the evidence that Mr Chandler gave when examined, cross-examined, and re-examined follows hereafter.

B. Examination

1. How Mr Chandler Came to Be Involved

684. Counsel for BMS noted that Mr Chandler was first approached in November 2020 with a view to becoming involved in this case. He asked Mr Chandler to describe the nature of that approach and what information, if any, Mr Chandler was provided with. The following exchange then occurred between Mr Chandler and counsel:

Mr Chandler:	*It's fairly typical for law firms to reach out to me to be an expert witness. I recall in that timeframe WilmerHale reached out to me, saying would you be interested in becoming an expert witness in a case? And I stopped them pretty abruptly and said, 'I'm rather busy now, I'm preparing for an appeal in the Delaware Supreme Court, so I just don't have time to give it – I don't want to do it unless I have the time.' So I referred them to my colleague, the late Justice Holland, who worked with me in the Wilson Sonsini office. And I think they went on and spoke to him and that's how he became involved.*
Counsel:	...[J]*ust in that context...Judge Holland passed away very shortly before his witness statement was to be delivered here, isn't that correct?*
Mr Chandler:	*He did. And so WilmerHale reached out to me and said, 'Bill, can you help us out? Can you step in his shoes and be a testifying*

witness in the case?' And I didn't want to leave them in the lurch, so I said yes, I would continue on and follow on with Justice Holland's work. And that's what I've done.

Counsel: *And in that context, I think what you did, as is apparent from your witness statement, is you gave a relatively short witness statement initially and you attached the late Judge Holland's report and you summarised, in effect, your agreement with his report, isn't that right?*

Mr Chandler: ...[C]*orrect.*

685. I mention this exchange for reasons that will become apparent later below.

2. Economic Interest

686. Counsel for BMS noted that in his oral evidence Mr Steele had started to address what he referred to as economic interest. Asked by counsel whether, under Delaware law, there is a property ownership concept of economic interest, Mr Chandler responded that he was not aware of it, stating:

> "*There are three types of ownership under Delaware law: One is beneficial or equitable ownership; one is legal or bare legal title ownership; and the third is all of those combined, where you own all of the interests, both the equitable or beneficial interest and the legal title interest. So, I'm not familiar with a separate property interest known as an economic interest. Economic interest is essentially an element, it's one element or part of owning the beneficial interest or the equitable interest in a property or asset.*"

3. *Hologic*

687. Turning to the *Hologic* case, counsel for BMS noted that counsel for Teva had suggested that it was a major omission in providing instructions to any expert in the present case not to tell that expert that the judgment made by the client was that a mistake had been made in respect of the later filed patent that was claiming priority from the first filed patent. Asked if he had any observation to make in this regard, Mr Chandler observed as follows:

> "*The only observation I would make is that it doesn't affect or change my ultimate opinion....Because we're being asked to opine whether, under Delaware law, BMS Co is the ultimate true owner of the patent in dispute. And so those issues about mistakes being made wouldn't affect the way a Delaware court would analyse, the legal framework that it would use to analyse is a party – in this instance BMS Co – the true beneficial owner of an asset that's legally titled in a separate entity. It wouldn't affect that analysis, so that's why I say it doesn't change my opinion*".

688. Counsel for BMS and Mr Chandler now engaged in a series of questions about who decided Hologic and what in fact it decided:

Mr Chandler: [The deciding judge, Judge] *Robinson's a very well known Delaware judge and also Delaware lawyer. She practised law as a lawyer first. She was a United States Attorney for the State of Delaware. She was later appointed as a Federal District Court judge and presided for many years in that capacity. So, a true Delaware lawyer.*

Counsel: *And insofar as this judgment is concerned, this is the United States District Court for Delaware....*[I]*n that context, can I ask you to confirm...what happens in the Federal Court when the Federal Court is required to consider concepts of Delaware law..?*

Mr Chandler: *Well, there's no federal common law. So, if the Federal Court in Delaware is looking to common law, it would look to the common law of Delaware, particularly if it involves a Delaware corporation, as it did here. So, Judge Robinson would have been doing what any Federal District Court judge in Delaware would do, she would look to Delaware common law to figure out how to determine the question presented. And here, the question presented is exactly like the question* [that has] *presented in this case, in my judgment, which is did Hologic, the parent corporation, possess a beneficial interest in the patent that was held solely in the legal title in the name of its subsidiary, its wholly-owned subsidiary? She looked at it the way a Delaware lawyer and a Delaware judge would look at it, which is what are the indications, the facts and circumstances that would support a finding that the parent company, Hologic, owned the beneficial interest in the patent in dispute? So, she mentioned things such as it had complete control and unfettered control over the patent and how it was used and deployed, whether it was licensed and enforced or assigned, that it made those decisions for its subsidiary, just like BMS Co in this case makes the very same decisions with respect to the patent here. So, Judge Robinson found that because those boundaries – she referred to it as the boundaries of the corporations – had been breached in that way, she found that it was essentially the equitable owner of the patent in question there, and so it gave her the right to say that 'Minerva, your effort to dismiss the case on the grounds that Hologic doesn't own the patent is not going to be granted, Hologic will be allowed to enforce its rights and seek an injunction against Minerva to prevent Minerva from infringing on that patent and the rights that go with that patent to sell or market' - I think it was medical products or something that were in issue....So, that was her ruling. And to me, it's also sort of noteworthy that Judge Robinson doesn't refer to any kind of written agreement or written assignment as being necessary, she applied the classic test for determining whether or not an equitable interest exists. And that interest is defined under Delaware law exactly as she wrote her opinion.*

Counsel: ....[I]*n that context, if you would just go…to ...the decision....a definition is identified there from* Digitech*, but which comes from the Black's Law Dictionary.... Can I ask you whether that is the definition that the courts of Delaware would apply when considering beneficial interest? ...*

Mr Chandler: *I think it says equitable title may be defined....as the beneficial interest of one person whom equity regards as the real owner, although the legal title is vested in another. And that's from* Digitech*. That's the classic definition under Delaware law of equitable or beneficial title.*

4. *Appraisal of Dell*

689. Turning next to the *Appraisal of Dell* decision, counsel for BMS noted that the principle in that case that "*There are circumstances under which equity can intervene not to change a statute or the policy behind it, but to prevent its application under circumstances....after weighing the harm, would weigh too heavily against one party and not heavily enough in favour of the other party. That's part of equity's intervention in Delaware*". Asked if he agreed with this statement of principle, Mr Chandler indicated that he did, "[a]*nd not surprisingly....It's a classic statement of*

Delaware law."

5. *Hollinger*

690. Turning next to the decision in *Hollinger*, counsel for BMS noted that in the specific context of *Hollinger* and §271, he had asked Mr Steele that "[N]*o statutory amendment was made to prevent the Courts of Equity engaging in the substantive exercise of review to identify who a beneficial owner was, isn't that correct?*" and received from Mr Steele the answer that "[T]*hat's correct. And it would be unlikely for a statute to exist out of the context of what that statute is governing that would so restrict it. Because that's the traditional difference between law and equity in Delaware.*" Asked by counsel if he agreed with Mr Steele's response, Mr Chandler indicated that "[H]*e's precisely right and I agree with him entirely. The legislature would never adopt a blanket statute that restricted the equity court in that fashion. It would be confined to the very limited circumstance they were trying to define. So I agree with him entirely*."

691. Counsel for BMS then noted that Mr Steele had also agreed with him when counsel put to him that "*Section 220, like Section 271, like Section 225, are providing statutory rights, but the provision of those rights does not impact the jurisdiction of the Court of Equity to identify who the beneficial owner is*.". Asked what his view was of this answer, Mr Chandler responded that he agreed with this response also.

692. Counsel for BMS turned next to Mr Chandler's second witness statement, where he treats with the *Hollinger* case, observing, amongst other matters as follows:

> "*Importantly, the court discussed Hollinger International's argument that Section 271 'does not apply to a sale of an asset by a wholly owned subsidiary unless the subsidiary's existence would be disregarded under the standard for piercing the corporate veil.' Id. at 371; accord id. at 373, 375. The court found there was no basis for veil-piercing between Hollinger International and the lower subsidiaries in the chain. Id. at 348, 371, 374–75. The court explained that the chain of subsidiaries was 'formed because they had valuable tax, financial, and liability-insulating purposes' and Hollinger International had 'maintained the corporate formalities necessary...to comply with...regulatory requirements.' Id. at 372. Therefore, under the stringent veil-piercing test, the corporate separateness would be respected. But the court's analysis did not end there.*"

693. Counsel then asked Mr Chandler to explain what significance he placed on the analysis in *Hollinger* and whether that is consistent with the jurisdiction of the Delaware equity courts. To this, Mr Chandler responded as follows:

> "[T]*he analysis that then Vice Chancellor Strine...went through in...Hollinger...was pivotal to his ultimate holding in...Hollinger....*[b]*ecause he ultimately concluded that the assets of Telegraph, which was at the end of the chain of subsidiaries, could be treated or acted as though they were actually the assets of Hollinger International. That reasoning allowed him to draw that conclusion or make that decision. And then he found that 271 wasn't triggered, because even if you did that, those assets did not constitute all, or substantially all, of Hollinger International's assets and so it didn't trigger 271's requirement that the shareholders of Hollinger International vote on that sale. And so he denied the request for an injunction to stop the sale, because he found that 271 wasn't being triggered. But his reasoning that led him to that conclusion was, in my judgment, was pivotal to the outcome that he reached. It also was acknowledged by the legislature; roughly a year later the legislature and the Corporate Law Council, which is the body of lawyers that monitor Delaware law and are constantly proposing when it should be changed, recommended to the legislature, which agreed, that 271 should be amended to basically adopt the reasoning and the outcome that Vice*

*Chancellor Strine had reached in...*Hollinger*....So, they did, they amended 271, creating a statement in it that says...if it's...a wholly-owned subsidiary of a parent corporation...the parent can treat those assets as though they were their own, even though they're not, for 271's purposes to make sure that 271 isn't being evaded in some way by a corporation. So that's the outcome of the case...*.[and] *for me, the reasoning of Vice Chancellor Strine was important to his ultimate conclusion.*"

694. Asked if Strine VC's reasoning was consistent with the extracts that counsel had put to Mr Chandler from Mr. Steele's evidence, Mr Chandler responded as follows:

"*Yes. Because I think what...*[Mr] *Steele was saying is that the legislature amended that statute. But that doesn't mean that the Court of Chancery could not engage in that same kind of reasoning in some other context outside of 271. In the context of 271, the legislature has codified it just to make sure that it's clear and certain for parties going forward. But that doesn't mean that they were forbidding or impeding the ability of the Court of Chancery in other cases unrelated to 271 to use the same reasoning that Vice Chancellor Strine used in the* Hollinger *case to just look at the practical reality. The practical reality is major corporations frequently set up subsidiaries, wholly-owned subsidiaries, to hold assets. That's quite common, it's quite typical. And so we should recognise that reality and not let some formalism prevent us from recognising that basic reality. That's what Vice Chancellor Strine was saying, that's what the Court of Chancery is known for and that is why the legislature would not try to impede it from making that same kind of analysis in other cases outside of 271 in Section 220, where they've codified it just to make it certain and clear in those instances.*"

6. Successor in Title

695. Counsel for BMS noted that Mr Chandler had accepted and endorsed the opinions of Judge Holland, particularly in relation to the concept of 'successor in title', and invited Mr Chandler to expand on this. To this, Mr Chandler responded as follows:

"*Justice Holland concluded, and I would reach the same conclusion, that Delaware would be persuaded by the decision of the court in* Fujifilm*, a decision by Justice Carr...and the decision by Judge Arnold in the* KCI *case, which was cited as precedent in...*Fujifilm*....Because it's consistent entirely with the way Delaware courts would approach this question, and that, is as the* Fujifilm *court held, and the* KCI *court held...the party who holds the entire beneficial interest in an asset, like a patent, should be treated as the successor in title, even though it doesn't hold the legal title at the relevant time...[and] that it should be...empowered to invoke rights of priority with respect to that patent, in accordance with the Paris Convention. The reasoning of those courts, both the* KCI *court by Judge Arnold and the Fujifilm court by Justice Carr, rely on the same principles that I think animate Delaware law, and that is, as they say in those opinions, that the substantive rights of the true property owner should be respected and legal formalities should not get in the way of respecting the true legal ownership rights of that beneficial owner. And that's precisely the way a Delaware court and Court of Chancery would look at it; it would not allow legal formalities to impede or interfere with the rightful ownership of the true owner, the beneficial owner. And so that's why I think Justice Holland concluded that here in this case, the fact that there is irrefutable and undisputed evidence that BMS Co controlled and directed the patent in question gave it the beneficial ownership interest that it held in the company, which it, after all, paid almost $8 million* [sic - billion?]*in cash for. And I think all those facts led Justice Holland, and in turn me, to the conclusion that it would be found to be the rightful beneficial and true owner under Delaware law. That conclusion then, it follows logically from that that it would be considered the successor in title and*

empowered to invoke priority with respect to that patent in accordance with the Paris Convention."

7. Beneficial Ownership of Inventions

696. Counsel noted that Mr Steele had agreed *"that under Delaware law...a company is entitled to the beneficial ownership of inventions made by its employees in the course of their employment*" and asked if Mr Chandler also agreed. Mr Chandler indicated that he did.

C. Cross-Examination

1. Mr Chandler's Instructions

697. In response to various questions from counsel for Teva concerning Mr Chandler's giving of evidence in this case, Mr Chandler indicated that:

(i) he had given expert evidence in court twice and provided expert evidence eight or nine times,

(ii) he believed that he knew the rules and restrictions relating to expert witnesses,

(iii) he was not tutored in what Irish courts would permit as expert opinion, "*but I submitted the statements, along with Justice Holland, which I thought were like Justice Steele's*",

(iv) he did not believe that he was given written instructions,

(v) he prepared his opinion based on the questions that he was told were going to be for the Irish court to decide and that his role was to be helpful to the court by offering his opinions to the court,

(vi) he did not receive any instructions other than oral instructions,

[I should perhaps note in passing that Mr Chandler, who was physically present in Dublin for most of his testimony, was asked to produce in court the documents containing his instructions while in Ireland and was later recalled as a witness online as the documents he needed to access were, I understand, in the United States. I turn to that later evidence later below.]

(vii) he was briefed by WilmerHale after Judge Holland passed away, at which time WilmerHale came to him and asked if Mr Chandler would help by continuing on from Justice Holland's work, and he agreed to do that,

(viii) he was provided by WilmerHale with Judge Holland's report and with all the documents that he reviewed,

(ix) as a general matter it is usual in the United States, as in Ireland, for an expert witness to be able to identify the information and instructions that s/he gets when providing an expert report,

(x) (in response to the question what issue he was told presented when approached by Wilmer Hale in November 2020) he did not quite recall, he remembered that they said 'We need to know if you would be willing to serve as an expert witness on Delaware law' and did not get much further because he quickly referred them to Judge Holland instead,

(xi) the issue of Delaware law in this case is "[t]*he ownership of a piece of property, a patent*" and whether there was beneficial ownership of same,

(xii) he did not know of any other issue of Delaware law that might have been relevant in November 2020 other than the one on which he has now given his opinion.

(xiii) following on his observation in his written statement that *"McCann FitzGerald LLP sought my expert opinion on the questions that had been*

presented to Justice Holland, taking into account the matters stated in the Golian Statement", he did not know if he had a letter of instructions but that he had "*the record that I was instructed over the phone that they needed a Delaware law expert to opine about what are the rules or the legal framework under Delaware law for deciding if a party owns a property interest beneficially or equitably*",

(xiv) he was "*sure* [that] *at the beginning*" he was told what property was involved,

(xv) he did not ask for any formal written instructions. "*As I said, I had the Holland report and all the documents that Justice Holland had reviewed. So, I was provided all of that. I also had two colleagues in my firm who worked with Justice Holland, associates at the firm, who were helping me and informing me, you know, what we needed to do to put together a new analysis or a new statement for me. So, I had all of that. And I had conversations with WilmerHale lawyers about what Justice Holland had done up until then and what they needed me to do to finish out the assignment*",

(xvi) in response to a question about what WilmerHale were telling him about what Judge Holland had done and what approach he had taken, that "[T]*hey weren't really telling me anything about what he had done already. They were explaining to me, and probably in response to my questions, about what was left to be done. And I didn't understand how many different jurisdictions were going to have to have statements and potential testimony, so the WilmerHale lawyers undoubtedly were explaining to me 'Well, you'll have to have a statement for Finland, you'll have to have a statement for Sweden, you'll have to have a statement for France'. So, that's what I think I was getting, was input from them about what I needed to do to finish out the assignment that Justice Holland had begun.*"

(xvii) in response to the question that "you *were getting your own assignment...being asked to...advise on beneficial and equitable ownership of property in Delaware*", that he was "*But of course, I already had the opinion of Justice Holland, with whom I totally agreed when I read his opinion and statement. So, it was more about how many times am I going to have to testify and where and when and will I have to provide supplemental statements to what Justice Holland has done or can we rest strictly on what Justice Holland has done? Those are the types of questions that the folks at WilmerHale were trying to help me with*."

(xviii) that he had a good relationship with Judge Holland,

(xix) when he got Judge Holland's opinion he was assisted by people who had assisted Judge Holland who provided him with "[r]*esearch assistance. I mean, if I needed to look at a case, they'd get me the case. If I asked them to sort of give me, you know, the shorthand version of what a decision was, they would do that. They helped me craft the statements the way associates typically help partners in drafting*", assisting him with "[v]*arious portions*" of the statement (Mr Chandler did not have a record of which portions).

2. Corporate Separateness

698. Counsel for Teva put it to Mr Chandler that **"***fundamental to Delaware law is the principle of corporate separateness*", that corporate separateness is "*a fundamental principle of Delaware corporate law*", Mr Chandler twice responded that "*It's an important principle of Delaware law*". Asked about exceptions to the principle, Mr Chandler accepted the four exceptions mentioned by counsel (§220, §271, the doctrine of veil piercing, and the appraisal statute) but indicated that there

were other exceptions. Asked to identify the principles that underpin those other exceptions, Mr Chandler responded as follows:

> "*The principles are that Delaware law is a flexible body of law and the Delaware courts are charged with maintaining that flexibility. And therefore, the courts of Delaware are empowered, particularly the Court of Chancery, to employ equity where the circumstances warrant or justify disregarding the separate corporate personality of an entity in order to do justice and to recognise the rights, for example, of a lawful owner or true owner, a beneficial owner. So, there are other instances, though, where the courts in Delaware, the Court of Chancery in particular, they won't disrespect separate personality. The only time you do that is when you're piercing the corporate veil. These other instances aren't really disrespecting the separate personality of the separate entities, it's simply saying that 'For practical reasons, we're not going to let that formalism intrude or impede upon reaching the just outcome'. So, that's why you have these exceptions that the counsellor has just mentioned, like in books and records cases, 271, the appraisal statute. But in other cases, like in double derivative cases, the courts have done the very same thing; they've said you can bring a double derivative action and the parent corporation will be treated as though it's the true owner of the claim or asset at the subsidiary level and be able to take that claim and pursue it, because the parent, in reality, really owns it or really controls it. So, that's an example that's beyond 220 or 271 and it's beyond the appraisal statute and it's beyond veil piercing. But that's another instance where a Court of Equity will say 'We're not disrespecting the separate entities, but we're going to recognise the reality here and treat these assets as though they actually are controlled by the parent corporation'. So, that's just one more instance.*"

699. Asked by counsel for Teva where "*this principle of the flexible body of law, maintaining that flexibility, applying equity where the circumstances warrant*" was set out in his report, Mr Chandler responded that it was not set out in his report or that of Judge Holland.

700. Asked by counsel for Teva which of the decisions referred to by Mr Chandler provides authority for the principle that he had identified, Mr Chandler responded that the Constitution of Delaware vests equitable powers in the Court of Chancery. Asked to name the case that identifies the posited principle as a principle of law that offers an exception to corporate separateness, Mr Chandler responded that the case of *Schnell v. Chris Craft Industries Inc*. came immediately to mind but accepted it was not mentioned in his report "[b]*ecause the flexibility principle isn't referred to*".

701. Asked if he knew that "*as an expert, when you come to assist the Court, you need to lay all of the relevant legal principles and information before the Court*", Mr Chandler indicated that he knew this and that he thought himself to have done that.

702. Asked to describe *Schnell* v. *Chris-Craft Industries Inc*., the following exchange transpired between Mr Chandler and counsel for Teva:

> Mr Chandler: ...[T]*he issue was the Board of Directors had moved the timing and the place for the meeting of a shareholder meeting. And technically they had the legal power to do that, under the statutory law of Delaware they had the right to do that. But by doing so, they were impeding the rights of shareholders who were intent on perhaps replacing members of the Board of Directors that they disagreed with. And so the Court there found that equity should intervene and deprive the directors of the power to move the Board meeting and the timing of the meeting and the place of the meeting so as not to thwart the efforts of shareholders to replace the Board of Directors.*

Counsel: *Those facts are very different from the facts of this case..?*

Mr Chandler: ...[V]*astly different....*

Counsel: . *...And...directors owe fiduciary duties not just to the parent company, but to the corporation itself....[so] if they act in breach of those duties, equity will clearly restrain them, isn't that correct?*

Mr Chandler: *Yes....*

Counsel: *And the principle that you've identified, apply equity where the circumstances warrant, that is a principle that, in its expression, implies that something inequitable is done to warrant the intervention of equity, isn't that correct?*

Mr Chandler: *Usually....*

Counsel: *Well...you're saying "usually", is there any circumstances where...some element of wrongdoing, unfairness, fraud, inequity is not involved?*

Mr Chandler: *I don't know of any off the top of my head.*

Counsel: *So, it's not just usual..?*

Mr Chandler: *Yes.*

Counsel: ...[C]*an you tell me, what is inequitable about a subsidiary owning the legal and beneficial interest in its assets? ....*

Mr Chandler: ...[O]*n its face, there's nothing inequitable about that.*

Counsel: *So, that's not a principle that could justify the intervention here for a court to say that the IP is equitably owned by the subsidiary..?*

Mr Chandler: *There's no facial reason for a court to do that....*

Counsel: [So]*...the principle of flexibility, apply equity where the circumstances warrant....has no relevance to the principle or...issue that this judge has to decide..?*

Mr Chandler: *That's up to this judge to decide, not for me....The conclusion I'm giving to the court, trying to be helpful, is that in Delaware law a judge would say that the parent company, BMS Co., was the owner of the beneficial interest in this patent that's in dispute that was legally titled in the name of BMS Pharma. That's the opinion I'm offering, trying to be helpful to the Court.*

Counsel: *...And the principle that you''ve identified which underlay that opinion...that is a principle which you now confess has no application to this case?*

[I cannot but respectfully note at this point that Mr Chandler said nothing of the sort. He was asked (see above) "[W]*hat is inequitable about a subsidiary owning the legal and beneficial interest in its assets?*" and answered "...[O]*n its face, there's nothing inequitable about that.*" The succeeding questions of counsel then proceeded on the basis that (i) he (counsel) had accurately summarised the alleged inequity presenting in this case (as will be seen later below I do not accept that he did) and (ii) consequently Mr Chandler's answer meant that the equitable principle he (Mr Chandler) had referred to had no application to this case. Mr Chandler, as will become clear in his later evidence, did see an inequity to present on the full facts of this case as they actually present, not as they were summarised by counsel].

Mr Chandler: *Again, I do not understand that. The principle that Delaware courts apply is they look at the facts and circumstances about how the parties treated the property or the asset and they look at whether the parties intended to divide the ownership between the title owner and the beneficial owner. That's what courts look at is*

> *those facts and circumstances that govern the relationship between the parties. And that's what Justice Holland did and that I am doing here, looking at the facts that are unrebutted and undisputed about the way that BMS Co and BMS Pharma, the relationship between those two entities and how they treated this asset in which BMS Co exercise all of the decision-making authority, had all of the legal resources at BMS Co, not at BMS Pharma and how all the directions and instructions it gave to BMS Pharma were followed by BMS Pharma, which it was required to do under Delaware law, because as a fiduciary principle, under the Anadarko case, the subsidiaries, directors and executive management must follow the directions and do what's in the best interests of the parent sole stoke holder. That's the opinion and that's the basis for the opinion.... It's correct to say that if...the only fact that a court is looking at is that the parent owns 100% of the stock, that, by itself, standing alone, would not lead a court in Delaware to say 'So the parent's the beneficial owner of the assets'. It takes other facts, other circumstances that the Court could then say 'That reflects the intention here of the parties, what they intended to do and here's how I can arrive at that, not by looking at the sole stock ownership alone, I have to have other facts.' That's the difference between Digitech and the...Hologic case. In Digitech you only had one thing - the fact that the parent owned 100%. And Judge Wright, the Federal judge, said that's not enough to find equitable title. But in Hologic, Judge Robinson had more than that; she had not only the fact of 100% ownership and the fiduciary obligation that the sub, you know, pays to the parent, but she had all the other facts, just like here, to lead her to the finding of the parent was really the equitable and beneficial owner. So, I agree with you that just standing alone, just owning the stock, by itself, is not enough to lead a court in Delaware to conclude. It would be one fact to consider, but it would take more.*

703. Springing from Mr Chandler's reference to "*facts that are unrebutted and undisputed*" counsel recalled the evidence of Ms Leung to the effect that BMS's control of its Irish subsidiary did not give it any interest in same,[5] he asked if Mr Chandler agreed with that. To this, Mr Chandler responded that this was "*beyond the scope of the opinion that I offered and that Justice Holland offered. I'm not looking at any other subsidiaries, I'm looking at just one....BMS Pharma. And I'm*

[5] The parties will recall that on her second day in the witness box the following exchange occurred between counsel for Teva and Ms Leung after counsel had brought Ms Leung to the financial statements of *Bristol-Myers Squibb Holdings Ireland Unlimited Company*:

Ms Leung:	...[W]*hat the document reads...is consistent with the statement I made yesterday that in certain circumstances...there may be exceptions to the general statement that I made....So, there are special circumstances. And as I testified yesterday, I did not recall, given the lateness of the hour and the activities of the day, that Bristol-Myers Squibb Holdings Ireland Unlimited Company is one of those special situations.*
Counsel:	*Ms Leung, your evidence yesterday was very particular; that they did own the assets of the Irish companies....*[and that] *the revenue belonged to BMS. That was very specific evidence you gave.*
Ms Leung:	*When...I testified to that yesterday, we had been speaking with respect of beneficial ownership. In reviewing these documents today and familiarising myself with Bristol-Myers Squibb Holdings Ireland Unlimited Company, I fully understand that ownership of intangible assets does not necessarily drive where income derived from those assets should be allocated, so those were different situations....*[T]*hose things you just brought my attention to are consistent with the statement I made yesterday that...when there are special situations and a business need...there may be differences....*

not going to opine on any other subsidiary, because that's beyond the scope of my expert testimony."

704. At this juncture, counsel for Teva turned to the issue of corporate separateness again. I am not sure that the exchange added much by way of illumination, certainly there was no change in Mr Chandler's evidence, save for the semantic difference that whereas in the morning Mr Chandler had stated the principle of corporate separateness to be "*an important principle of Delaware law*", he now accepted it to be, as posited by counsel "*a cardinal principle of law in Delaware*". The two (counsel for Teva and Mr Chandler) also touched, in the following terms, on the fact of Delaware being a corporate-friendly state and of how asset partitioning operates:

Counsel:	*You give many talks and lectures on Delaware law, don't you?*
Mr Chandler:	*...I do.*
Counsel:	*And part of what you're doing is explaining to people how corporate-friendly Delaware law is...?*
Mr Chandler:	*I'm not sure that's the theme or the tenor, but you could perhaps draw that conclusion....*
Counsel: .	..[O]*ne of the things that you have identified repeatedly is the principle of corporate separateness....*[a]*s a cardinal principle of law in Delaware....*[a]*nd that the principles of corporation law in Delaware are certain..?*
Mr Chandler:	*Yes....*
Counsel:	[O]*ne of the matters that flows from...*[the principle of corporate separateness] *is asset partitioning..?*
Mr Chandler:	*Yes, that's one.*
Counsel:	*And that means if the assets are in the subsidiary, they're in the subsidiary and if they're in the parent company, they're the parent company*['s]..?
Mr Chandler:	*That's what it generally means.*
Counsel:	*And you know that in bankruptcy, when the subsidiary goes bankrupt, the assets of the subsidiary are available for the creditors, isn't that correct?*
Mr Chandler:	*I'm not a bankruptcy expert, but my general understanding is that they would be used for the creditors unless there were claims of priority to those assets by others. But again, I'm not an expert in bankruptcy law....*

705. I believe that the point that counsel for Teva might have been trying to get at here was that if corporate separateness is not scrupulously observed in Delaware's law of equity, then that might cause difficulties in other areas of Delaware company law, such as what is to happen to company assets in the event of a company insolvency. However, (i) I am not tasked with the exercise of seeking to resolve all aspects of Delaware law, (ii) there is no bankruptcy issue presenting in this case, and (iii) if the Delaware laws of equity as they presently operate present some risk as regards whether Delaware is perceived as a corporate-friendly state and/or whether creditors are adequately protected under Delaware law in the event of company insolvency, then that is (a) a risk that, as a matter of fact and law, presents and I cannot change that, and (b) a matter possibly for the people and State of Delaware to consider and, if they wish, to address (*i.e.* not for me).

706. It may also be that counsel for Teva was seeking to suggest that Mr Chandler cannot be right in his understanding of the laws of Delaware because that would be inconsistent with how the law of Delaware operates in other regards. If so, I am not convinced by this logic, both because of Mr Chandler's expert evidence as to how the law of equity operates in Delaware and also because I do not believe that every branch of any legal system is going to be entirely consistent in all respects. (Just to give one example: on the day before I wrote this paragraph I refused a costs application in a family law case because costs are typically not awarded in family law cases; yet in the commercial courts it remains the case that costs continue typically to 'follow the event'. That is two areas of a

coherent and sophisticated legal system doing different things for different reasons as regards the same issue: costs. To expect complete consistency between all branches of the law in how they operate seems to me to be, with all respect, an expectation that will never, and likely can never, be satisfied).

3. Control

707. Turning next to the issue of control, counsel for Teva noted that when giving evidence in Finland (in parallel proceedings to the present proceedings), Mr Chandler had referred to how a parent corporation may direct and control subsidiary actions. This led to the following exchange between counsel for Teva and Mr Chandler:

Counsel:	*That is, of course, subject to the principle that the directors* [of the subsidiary] *still owe a broader fiduciary duty...?*
Mr Chandler:	*....Yes...they owed* [*sic* – 'owe'?] *a broader fiduciary obligation, not only to the parent corporation....but...to positive law. I mean, if the parent corporation was to try to direct the directors of a subsidiary corporation to break the law, violate positive law, their fiduciary obligation would prevent them from doing that, cause them not to do that.*
Counsel:	*And also, where the company is insolvent, those duties intervene..?*
Mr Chandler:	...[U]*nder Delaware law, when a company is insolvent, the duties run not only to the stockholders, it runs to the creditors....They become then empowered to enforce those fiduciary obligations.*

708. Summarising his understanding of some of Mr Chandler's evidence to this point, counsel identified three principles that Mr Chandler had identified, "*First, corporate separateness; second, formalities may be set aside in certain circumstances; third, that when considering a parent corporation's ability to exercise actual control over its subsidiary and assets and operations and the subsidiary is expected to operate solely*", positing that in paragraph 2 of his first witness statement Mr Chandler had coupled these principles solely with BMS Co's 100 per cent ownership of BMS Pharma and arrived at a similar conclusion to Judge Holland (as to where beneficial title would be construed by a court to lie). Paragraph 16 of Mr Chandler's first witness statement states as follows:

> "...[A]*s explained in the Holland Expert Report, it is settled law that, while Delaware generally recognizes the separate and independent existence of wholly- owned subsidiaries, those formalities are set aside in certain instances. Delaware statutory law has codified that principle when considering a parent corporation's ability to exercise actual control over its subsidiary's assets and operations. Delaware cases have confidently affirmed that – given the practical and operational benefits that a wholly-owned subsidiary affords the parent – the subsidiary is expected to operate solely for the parent corporation's benefit. As a result, the parent corporation may direct and control the subsidiary's actions. Applying these principles in view of BMS Co's 100% ownership of BMS Pharma, I agree with Justice Holland that BMS Co had the right to cause its wholly owned subsidiary to assign to BMS Co the right to claim priority from the first-filed patent application.*"

709. The following exchange now occurred between counsel for Teva and Mr Chandler:

Counsel:	*So, your conclusion is based on those principles and the 100% ownership? That's what it* [the paragraph] *says*.
Mr Chandler:	*That's what that paragraph says....*
Counsel:	*And that is your evidence. Or is it?*
Mr Chandler:	*Well, my testimony is that those principles, combined with the facts*

that I say are undisputed facts about the control that was exercised by BMS Co over the patent in question, over the management and directors and over how BMS Pharma's operations actually were conducted, were all conducted by BMS Co, and the employees were BMS Co employees, those facts, added to those principles, lead me to my conclusion and led Justice Holland to his conclusion.

4. Beneficial and Legal Title Under Delaware Law

710. Counsel then moved to para.17 of Mr Chandler's first statement, where he states as follows:

"*...Justice Holland fully and accurately described the distinction between 'beneficial' title and 'legal' title under Delaware law. While one party may hold legal title to an asset, the asset's beneficial owner is the ultimate decision maker. Similarly to Justice Holland, I would conclude from the Golian Statement that BMS co-established a practice of resting legal ownership of certain intellectual property assets with its wholly-owned subsidiaries, including in particular BMS Pharma, while retaining beneficial ownership of, and its attendant control over, those assets. Mr. Golian's employment post-dated BMS Co's adoption of that policy, and he was not part of the 24 October 2001 email chain which described it. However, that policy was in place when he commenced employment with BMS Co the following year, and he was aware of it, and he has stated that it reflects his experience of BMS Co being the decision maker and having control over how the intellectual property assets of its wholly-owned subsidiaries are to be held and managed. Furthermore, the Golian Statement confirms that BMS Co's policy described above and its attendant control over BMS Pharma's intellectual property assets remained the state of affairs as of the date of the later-filed patent application.*"

711. Counsel then recalled that in his earlier testimony Mr Chandler had distinguished between three types of ownership, "*the beneficial, the bare legal title and then you said both*". The following exchange then ensued between counsel for Teva and Mr Chandler:

Counsel:	*Do you know what the definition in Black's Dictionary of* "legal title" *is?*
Mr Chandler:	*I don't know off the top of my head.*
Counsel:	*And legal title, in the ordinary way, includes the legal and beneficial ownership, isn't that correct?*
Mr Chandler:	*It might, colloquially –*
Counsel:	*No, no, no....Not it might....In the ordinary way, unless there's a distinction made, it is understood as covering the legal and beneficial.*
Mr Chandler:	*I would agree that it could be used that way. But when you say "*bare legal title*", most people understand you're talking about the entity that's just the record owner....*
Counsel:	*...I'm not asking you about bare legal title. We all know what that means....Where the term* "legal title" *is used, unless beneficial title is referred to and a distinction is made, it is understood as including beneficial title.*
Mr Chandler:	*Not always....*
Counsel:	...[Y]*ou're aware of the definition, I take it, in Black's Dictionary..?*
Mr Chandler:	*I am.*
Counsel:	...[T]*hat says: "Legal title - a title that evidences a parent ownership but does not necessarily signify full and complete title*

or a beneficial interest."

Mr Chandler: *Ah, it does say that. Doesn't necessarily include – ....*[T]*hen I agree with that.*

712. Counsel for Teva moved next to the segment of the above-quoted extract from Mr Chandler's statement where Mr Chandler states that,

> "*Similarly to Justice Holland, I would conclude from the Golian Statement that BMS co-established a practice of resting legal ownership of certain intellectual property assets with its wholly owned subsidiaries, including in particular BMS Pharma, while retaining beneficial ownership of, and its attendant control over, those assets*",

at which point the following exchange occurred between counsel and Mr Chandler:

Counsel: *So, you weren't just referring to BMS Pharma, you were referring to its subsidiaries more generally, isn't that correct?*
Mr Chandler: *No.*
Counsel: *Is that correct?*
Mr Chandler: *No, I'm referring especially to BMS Pharma.*
Counsel: *Especially. But the word "*especially*" incorporates, as I understand it, incorporates that it also involves others, isn't that right?*
Mr Chandler: *Not in my lexicon.*

5. Hearsay

713. Counsel for Teva moved next to the segment of the above-quoted extract from Mr Chandler's statement where Mr Chandler states that,

> *Mr. Golian's employment post-dated BMS Co's adoption of that policy, and he was not part of the 24 October 2001 email chain which described it. However, that policy was in place when he commenced employment with BMS Co the following year, and he was aware of it, and he has stated that it reflects his experience of BMS Co*.

714. Counsel for Teva then queried whether such reliance on Mr Golian's remarks, accepted by Mr Chandler to be part of "*the irrefutable and indisputable evidence that underlies your conclusion*" would be in breach of Delaware's rules on hearsay. Mr Chandler indicated that "*It may have been, yes*".

715. I admit to some surprise at this line of questioning. Mr Chandler made it clear in his statement that he had regard to the appendices to Mr Golian's Statement. Those appendices included e-mails from October 2001 regarding assets held in BMS Pharma and Teva accepted, in correspondence of 25th July 2022, that these e-mails would be evidence in the present proceedings.

6. BMS Policy

716. Counsel pointed next to the reference in the above-quoted extract from Mr Chandler's witness statement to BMS "*policy*". Asked what he meant by this reference to "*policy*", the following exchange ensued between Mr Chandler and counsel for Teva:

Mr Chandler: ...[T]*he policy and practice of BMS Co –*
Counsel: *Well, which it is now; are you talking about a policy or a practice..? ....*
Mr Chandler: ...[A] *policy is...a general statement of what a company will do*

ordinarily in the routine conduct of its business....A practice is just the practical way they go about conducting or operating their business.

Counsel: ...[W]*hat do you regard as...BMS's policy here?*

Mr Chandler: *The policy that I refer to is BMS would, when acquiring a company, its policy would be that it...rename the company – BMS Pharma, for example, in this case – and would use it as a repository of the assets that it was acquiring in that acquisition. So, when it acquired DuPont Pharma, the assets were deposited in the holding company – I'll use that term – of BMS Pharma and that's where they resided. And they could be directed and controlled by BMS Co, they could be assigned, they could be licensed, they could be sold, they could be – they had total control over the use and deployment of those assets, that's what I meant.*

717. Asked where he saw the policy, Mr Chandler at first indicated that he had seen it in the Golian statement or the Mathias statement. Asked if he got oral instructions from WilmerHale suggesting that such a policy existed, Mr Chandler responded, "*If I did, I don't recall it.*" Ultimately Mr Chandler indicated that he had misspoken and that (i) he had relied on the Mathias statement in proceedings other than in Ireland and that when doing his report for Ireland he did not rely on Mathias and was not relying on it before me, and (ii) he was relying on the Golian statement in his statement. I do not know what counsel for Teva intended to achieve with this line of questioning: the Golian statement has appended to it the emails that identify the purported policy. In fact, counsel for Teva now brought Mr Chandler to the Golian statement, acknowledged that "[T]*he e-mails are set out in the statement. They're also attached as an appendix*" and then engaged in the following exchange with Mr Chandler:

Counsel: ...[W]*hat...in that e-mail* [of 19th October]*, suggests that there's beneficial ownership in BMS? ....*

Mr Chandler: "*BMS Pharma houses most of the intangibles.*"

Counsel: *....What does, in that statement, suggest that BMS Pharma doesn't have beneficial ownership?*

Mr Chandler: *It suggests, to me, that it just houses them, they're not the true owner, they're holding them.*

Counsel: *So, on that basis then, equity is going to intervene, on the basis of an e-mail of 19th October stating a fact that BMS Pharma houses the IP and your flexible principle of equity which underlies your report, that triggers that principle, is that correct?*

Mr Chandler: *Among other things.*

Counsel: *I see. And now could we look at the next e-mail* [of 24th October]..? "Patents and trademarks related to the Pharmaceutical business - Maintain legal ownership in Bristol-Myers Squibb." *What, in that e-mail, suggests that beneficial ownership is elsewhere?*

Mr Chandler: "Maintain legal ownership".

Counsel: *And on that basis, that suggests to you –*

Mr Chandler: *Partly.*

Counsel: *Partly? Is there any suggestion of beneficial ownership residing elsewhere?*

Mr Chandler: *It also says:* "This is the entity where they currently reside".... "So this should involve only a name change"....*So, they're putting them there and they're just changing the name and they're giving them the legal ownership to house intellectual –*

Counsel: *...No, no, it says* "maintain". "These resided in this company." *Maintain legal ownership, change the name. There is no*

suggestion that beneficial ownership is going elsewhere, none.

Mr Chandler: *There's no suggestion that the legal title is going elsewhere. That's what's staying with Pharma.*

Counsel: *I think* [BMS] *Pharma had...and presumably you know this...both...legal and beneficial title at this stage? ....*

Mr Chandler: *I'm not aware that they had the equitable title....*

Counsel: *Were you told that there was an assignment from the inventors to BMS Pharma?*

Mr Chandler: *Yes....*

Counsel: *...And were you told of later assignments of this intellectual property? ....*

Mr Chandler: *I was....*

Counsel: *When?*

Mr Chandler: *Probably in May* [2023]....

Counsel: *So, you gave an opinion in April 2022, you gave a second opinion and nobody had ever informed you that there was a subsequent assignment of BMS Pharma's rights to BMS?*

Mr Chandler: *I think that's the rough timing of it....*[T]*he interesting thing is, though, the fact that there were later assignments only strengthens my opinion.*

Counsel: *....Can you think of any hypothetical fact that would undermine or weaken your opinion? ....*

Mr Chandler: *...I assume that if there was some document that said BMS Pharma really is the true owner and...has all the equitable rights to these patents, if I saw some document like that, that would give me pause.*

Counsel: *And would that be a principle that you would apply in respect of any wholly-owned subsidiary? .... In other words, a wholly-owned subsidiary that's under the direction of the parent, must do what the parent tells it, it has assets, would you believe that those assets are beneficially owned by the parents, unless you saw a document of the type you've just mentioned?*

Mr Chandler: *No, it would always depends on the facts and circumstances. Every time you're making a determination about a division of title like this between a beneficial owner and a legal titleholder, it depends on the facts and circumstances and how the parties dealt with the asset and how the parties structured their relationship and how they dealt with each other. So, no single fact is going to be determinative, usually. It's a very fact-intensive analysis.*

Counsel: *And where is that stated in those terms in your report?*

Mr Chandler: *It isn't.*

7. The Nature of the Inequity Presenting

718. Continuing with the just-described line of questioning, counsel turned next to consider with Mr Chandler the nature of the alleged inequity presenting that a court of equity in Delaware would see fit to intervene and remedy, asking what would be inequitable about BMS Pharma maintaining the beneficial ownership which it had?

719. This question in one form or another was posed a number of times and yielded the following answers:

Mr Chandler: [1] *Other than that BMS Pharma didn't pay the almost $8 billion for the asset. It seems to me that the one that really paid the $8 billion in cash has a strong claim to being the beneficial owner, or at least that's in the world I live in.*

...

[2] ...[A]*dd in the facts that I've just described for you about how BMS Co intended for that asset to be held. It intended it to be held strictly as a legal title asset that it would be controlling and making all of the decisions for. And in turn, BMS Pharma followed those directions to the letter, they never challenged them, they did exactly what they were told to do with respect to that asset. That's also consistent with what I've said earlier; they were sort of required to do that, that was their fiduciary obligation as well.*

...

[3] [T]*he inequity would be that the true owner of the property...BMS Company, would be deprived of that ownership interest if equity did not intervene here to recognise the reality that it was the true beneficial owner of the asset....That would be the inequity.*

...

[4] *Here, the inequity would be you would be depriving the true owner of its ownership rights if you didn't recognise that it had established a relationship with its subsidiary whereby it exercised total control over that subsidiary's asset, the patent in question. And so it determined that it wanted to maintain this division of ownership for business reasons. And all I'm saying is what the inequity would be here is if you failed to recognise that. In many other subsidiary/parent relationships, there wouldn't be any inequity, because the parent may want the legal title and the beneficial title to be residing in the subsidiary. That may be true in lots of cases, I'm sure it is. This is the case that's an exception to that general proposition.*

...

[5] ...[T]*he sheer ownership of 100% of the stock of BMS Pharma....doesn't, by itself, constitute a transfer of the beneficial ownership. It would be the other circumstances surrounding the way they dealt with each other, the parent and the subsidiary, and with this particular asset especially and how they organise the relationship. That was all done to make sure that BMS Co maintained and kept the beneficial rights of ownership*.

720. When it came to [5] and his reference to things being done to make sure that BMS Co "*maintained and kept the beneficial rights of ownership*", counsel asked <u>when</u> did BMS Co get "*the beneficial rights of ownership*", positing rightly that "*To maintain and keep something, you must have it.*" At this point the following exchange occurred between Mr Chandler and counsel for Teva:

Mr Chandler: *From the very beginning....*[T]*he minute they began organising Pharma and renaming it BMS Pharma, all of the instructions were coming from BMS Co down to the subsidiary – and all of its employees, by the way, are, as I understand it, BMS Co employees and directors – and they're instructing them how the assets are*

going to be titled, that the existing patents are going to be titled in the name of Pharma, future patents are going to be, instead, titled in the name of BMS Co. So, the parent is controlling completely how the subsidiary deals with that piece of property. That's the moment in which, you know, to a judge, I would say the relationship from the beginning was one where Bristol-Myers Squibb, the company, was saying 'We're in control, we are the beneficial owner of this asset, you're simply holding the legal title, which we can dip into and take as we wish and do with as with we wish'.

Counsel: *So, from the moment it acquired and started issuing instructions, it became the beneficial owner, is that correct?*

Mr Chandler: ...[Y]*es.*

Counsel: ...[A]*re you seriously saying to this Court that's a principle of Delaware law?*

Mr Chandler: *Yes.*

Counsel: *So, every corporation that acquires a wholly-owned subsidiary and issues directions to it, which the courts have repeatedly said it can do, it, by that acquisition and by those directions, becomes a beneficial owner of the assets of the subsidiary?*

Mr Chandler: *Depends.*

Counsel: ....[D]*o you think that might be of concern to Delaware corporations?*....[This question went unanswered in what was a rapid exchange between counsel and Mr Chandler]....

And there is no case in Delaware law or in the Delaware code or in...[a] *Delaware textbook that says that* [i.e. acquisition and issuance of directions] *results in a transfer of beneficial interest in assets the subject matter of those instructions?*

Mr Chandler: ...[I]*t doesn't say that, because it depends on the circumstances in every case.*

8. Some Cases Relied Upon

721. Counsel turned next to a consideration of certain of the cases that Mr Chandler relied upon in his witness statements. It is probably most useful just to name the cases in question and to quote Mr Chandler's explanation to counsel as to why he thought the case would be of use to me in coming to my judgment:

Lynch v. *Gonzalez*

Mr Chandler: [When it comes to this case] *I'm trying to illustrate for the Court how the Court of Chancery goes about determining whether a party has beneficial ownership interests in property or only legal title interest. That case is just an example, because I thought it was useful, because there Gonzalez had actually titled things literally in the name of Mr. Lynch and it looked like 'Aha, you've given him the ownership interest'. And then later Mr. Lynch goes rogue and tries to take the company away from Mr. Gonzalez, so Mr. Gonzalez sues in the Court of Chancery and says 'I'm the true beneficial owner, Mr. Lynch is trying to steal my company from me'. And so the Court goes through a long, lengthy analysis of all the factors that, when they did first this, Gonzalez never intended Mr. Lynch to own the company outright, he intended him only to have the legal title, so that when they tried to do business in*

Argentina they met the requirement that someone has to have Argentinian citizenship, which was Mr. Lynch. And so at that was the intention. And it was never intended to give him full ownership. So, the Court goes through this lengthy analysis and says 'Look at all the facts here. Mr. Gonzalez did this just because of this need to have someone in Argentina who had Argentina citizenship. And even though he signed these documents that conveyed what looks like full title, it wasn't really full title, it was just the legal title; he was retaining for his own benefit and trying to protect, for his own benefit, the interests of the company that he started'....[T]*hat was my reason for citing this case; I thought it was a good illustration of how the Court of Chancery would go about it. In this case, I think the Court of Chancery, if it were sitting, would go about the analysis in the same way.*

Taylor v. *Jones*

Mr Chandler: ...[A]*gain, it illustrates how a court in Delaware would apply the issue of equitable ownership or beneficial ownership. And that's one of the issues in this case, I thought....That was a case involving, I think, the two sisters who held title to real property and....one sister was given legal title so that she could get a loan with a bank or something and then she tried to deprive her other sister of the right to the property.*

Cartanza v. *Lynn*

Mr Chandler: ...[I]*n Delaware...licence plates that go on the back of cars are very valuable if they have a low number. The lower the number, the more valuable they are....And I think Mr Cartanza collected very low licence tag numbers. And he put those – you have to have them on cars. So, the more you collect, the more cars you have to have. So Mr Cartanza...placed one of these very low digit tags on the car of, I think it was his daughter-in-law...and then later she tried to claim that it was her tag and that she owned it. So, the Court of Chancery...did the typical beneficial ownership analysis and found that he really didn't intend to convey the full title, just the legal title, by placing the tag on her car and ordered it to be restored to the true owner*.

Danvir Corporation v. *Wahl*

Counsel: ...[T]*hat was also a case where somebody placed shares of a company in the hands of another person and the issue was whether they were intended to get beneficial title, isn't that correct?*
Mr Chandler: *That's correct.*
Counsel: *And again, no question of corporate separateness?*
Mr Chandler: *Again, no question of corporate separateness, because there's no connection between the two ideas.*

9. Invoking Mr Holland

722. Counsel for Teva noted that "[A] *number of times in your evidence, Mr. Chandler, you kept saying 'I believe this and I believe...*[Mr] *Holland would be of the same view*"". Counsel put it to Mr Chandler that it was "[o]*dd for an expert witness to ascribe a view to another person who is not*

giving evidence and who now, unfortunately, is dead. Why would you do that?". To this, Mr Chandler responded that he had answered so "[b]*ecause I've read Justice Holland's statements. I agree with him entirely. I just believe that he would hold the same conclusions that I do about this case*." Asked if this last point was "*offered to the Court as some reinforcement of...*[Mr Chandler's] *opinion*", Mr Chandler indicated that "*It's just recognising the reality that, unfortunately, Justice Holland isn't with us and can't give his opinion himself*". All this said, when counsel put to Mr Chandler that "[T]his is your evidence", Mr Chandler responded "*Oh, absolutely*", and again stated a minute or two later that "*I've spent 50 years building my reputation and I don't give my reputation away. So, whatever opinion I give, it's going to be my opinion....*[but] *I'm glad that I am giving the same opinion that Justice Holland is, because I have great respect for him...and so I'm just glad that I'm not disagreeing with him. But occasionally I did* [though not in his evidence in this case]."

10. Some Additional Authorities

723. Counsel turned next to consider a few decisions to which Mr Chandler had not referred in his evidence.

i. *NAMA*
(*NAMA Holdings, LLC* v. *Related WMC LLC,* 2014 WL 6436647 (Del. Ch.))

724. This was a case involving a claim for tortious intervention by a parent in the activities of its subsidiary, and features the following observations:

> "*A third and related policy is the practical recognition that although a parent and a controlled or wholly owned subsidiary are separate entities, the parent has a substantial economic interest in the profit-making activities of its subsidiary. As a result, a parent and subsidiary can be expected to consult on matters affecting the subsidiary and to make decisions on behalf of the subsidiary*".

725. After counsel for Teva read these lines aloud, the following exchange occurred between him and Mr Chandler:

Counsel:	...[T]*hat is recognised in Delaware law and that doesn't give rise to any question of beneficial ownership in the assets, isn't that correct?*
Mr Chandler:	*That alone does not.*
Counsel:	*So, the consulting and the direction in relation to the subsidiary is not a factor that has ever resulted in the blurring of this corporate separateness, isn't that correct?*
Mr Chandler:	*If it's the only factor, no.*

ii. *Doberstein*

726. In *Doberstein*, the suggestion was there should be a reverse piercing of the corporate veil, the court observing as follows:

> "*Doberstein claims that, despite Greenplate's otherwise limited liability, I should pierce GP's corporate veil and hold him individually liable for his allegedly fraudulent conduct. 'To state a 'veil-piercing claim,' the plaintiff must plead facts supporting an inference that the corporation, through its alter-ego, has created a sham entity designed to defraud investors and creditors'.*"

727. After counsel for Teva read these lines aloud, the following exchange occurred between him and Mr Chandler:

Counsel:	*That's a principle I expect that you accept and wouldn't demur from?*
Mr Chandler:	*Correct.*
Counsel:	...[C]*an I ask you, is there anything in the facts that you are aware of here that involves either BMS or BMS Pharma engaged in a sham entity designed to defraud investors and creditors?*
Mr Chandler:	*No.*

iii. *Top Victory*

728. Counsel turned next to the *Top Victory* case. There, Top Victory Electronics, Co. and Envision Peripherals, Inc. brought an action for declaratory judgment of non-infringement of seven patents related to digital televisions. The defendants moved to dismiss for lack of standing, and therefore lack of subject matter jurisdiction. The second defendant also moved to dismiss for lack of personal jurisdiction. In the course of his judgment, Breyer J. states, amongst other matters, as follows:

> "*One district court has found that the parent of a patent-holding subsidiary can be an equitable title holder to the patent, with standing to seek equitable remedies.* See Pipe Liners, Inc. v. Am. Pipe & Plastics, Inc., *893 F.Supp. 704, 706 (S.D.Tex.1995) (finding standing was proper where a parent owned a patent-holder subsidiary, where the matter would proceed regardless of whether the parent were joined as plaintiff). Other district courts have declined to follow this reasoning, however, instead holding that "a parent [corporation] does not have equitable title in a patent solely by virtue of its ownership of the subsidiary."* Steelcase, Inc. v. Smart Techs., Inc., *336 F.Supp.2d 714, 719 (W.D.Mich.2004);* accord Beam Laser Sys., Inc. v. Cox Commc'ns., Inc., *117 F.Supp.2d. 515, 520–21, 520 n. 6 (E.D.Va.2000) (noting that the Federal Circuit has only recognized equitable title to a patent in a matter involving a contract assigning patent rights to an invention that had yet to be discovered at the time the contract was formed). That a corporate parent's subsidiary owns a patent is not enough to establish that the parent has rights in the subsidiary's patents.* See Spine Solutions, Inc. v. Medtronic Sofamor Danek USA, Inc., *620 F.3d 1305, 1317–18 (Fed.Cir.2010) (holding that where nothing in the record indicated that the parent was an exclusive licensee of the patent, the court could not exercise jurisdiction over the parent). And the Federal Circuit has not held that a corporate parent inherently owns equitable title in a subsidiary's patents.* See Beam Laser Sys., *117 F.Supp.2d at 520 n. 6. Moreover, corporate law sets clear boundaries between parents and subsidiaries.* See Quantum Corp. v. Riverbed Tech., Inc., *No. C. 07–04161, 2008 WL 314490, at *1–3 (N.D.Cal. Feb.4, 2008);* Steelcase, *336 F.Supp.2d at 719;* Beam Laser Sys., *117 F.Supp.2d at 519–20. This Court has held that even if the companies are closely operated and the parent purports to act on behalf of the subsidiary, a parent does not have standing in a suit involving patents held by a subsidiary without a showing that boundaries between the corporations have been breached.*"

729. Asked by counsel for Teva if he was familiar with this last-mentioned principle, Mr Chandler responded "*I am. That's the* Hologic *case*".

iv. *Buechner*

730. Counsel turned next to the *Buechner* case. That was an action against a non-resident German corporation for damages based on its alleged failure to compensate plaintiff properly while he was in its employ, for failure to make promised payments upon termination of his employment, and for damages based on its action in preventing the plaintiff from taking a position in the United States upon his leaving its employ in Germany. In the course of his judgment, Southerland C.J., for the Supreme Court of Delaware observed as follows:

"*It is argued that German Bayer, notwithstanding the sale to Canadian Bayer, is still the equitable or beneficial owner of the Mobay shares. This contention, which completely disregards the separate corporate existence of Canadian Bayer, is based upon the rule that the stockholders of a corporation are the equitable owners of its assets. General statements to that effect may be found in the decisions....This is only an indirect interest, however. 'The shareholder's essential right is to share in the profits and in the distribution of assets on liquidation*".

731. Asked if there were any elements of this that he disagreed with, Mr Chandler responded "*Those general propositions, I don't disagree with*".

v. *Fletcher, Cyclopedia of the Law of Corporations*

732. Counsel next turned briefly to the *Cyclopedia of the Law of Corporations*, Mr Chandler accepted (i) the proposition therein, referred to by counsel for Teva in the following terms: "*A person who voluntarily adopted the corporate form to engage in a business may be deemed to be precluded from asking courts to disregard that form merely because the person is disadvantaged by its use*", and (ii) that that proposition has been cited with approval "*in quite a number of cases, including in the chancery decision in Delaware in 2009 in the CME Group* [case]".

733. The following exchange now took place between counsel for Teva and Mr Chandler:

Counsel:	*So, if you choose a corporate form, you're stuck with that corporate form..?*
Mr Chandler:	*That's a general proposition, and I agree with it.*
Counsel:	*Absent some inequity or wrongdoing in which, in certain circumstances, a court may intervene?*
Mr Chandler:	*Correct.*
Counsel:	...[Y]*ou subscribe to that principle?*
Mr Chandler:	*Yes.*
Counsel:	*And if there is no inequity, in this case, in BMS Pharma having the beneficial interest in the assets, you would accept there is no basis for a court intervention?*
Mr Chandler:	*No, I wouldn't agree. Because there are circumstances here where I think there is an equity, and that's the beneficial ownership interest of the parent corporation in one of the assets of the subsidiary. That doesn't require, at all, interfering with the corporate separateness of BMS Pharma and BMS Co....*
Counsel:	*Well, I'll put it on a hypothesis, which I thought I had done, but I'll repeat it. If the Court were to find that there is no inequity, then you accept that there is nothing that would trigger the intervention of the Delaware courts to hold that the beneficial ownership is in BMS?*
Mr Chandler:	*I don't understand the question. And I'll just answer it by saying if the court finds that there's no inequity in denying the beneficial owner it's true interest, then I accept that ruling. I just think that there would be an inequity if you deny the true owner its true ownership interests in an asset.*

734. This last sentence was almost a throwaway comment by Mr Chandler, yet to me it seemed to capture succinctly, in Mr Chandler's expert opinion, the inequity that he perceives that the courts of Delaware, in Mr Chandler's expert opinion, would exercise their equitable jurisdiction to remediate.

vi. *Pauley Petroleum*

735. Counsel turned next to *Pauley Petroleum* and to the following observations therein, at 373:

> "Pauley *contends that a corporate entity is not sacrosanct for all purposes, and the cases to which I have already referred so indicate. But we must deal here not from an ad hoc notion as to the most reasonable way to compel a Delaware corporation to submit a dispute to a judicial forum. Certainly in the normal course of events a corporate entity must be regarded as more than a mere formality. It is an entity distinct from its stockholders even if its stock is wholly owned by one corporation. Buechner....And this is true here*".

736. After counsel for Teva read these lines aloud, the following exchange occurred between him and Mr Chandler:

Counsel:	*That's a principle...you're familiar with and you wouldn't demur from?*
Mr Chandler:	*I am familiar with it. I would not disagree with it. And I want to make sure that the Court understands that nothing in Delaware law requires you to say that you are disrespecting the separate corporate personality of a subsidiary if you are recognising that the parent corporation owns the beneficial interest in certain assets in that subsidiary. That does not in any way diminish or disrespect the corporate separateness of each entity. That's the point, I think, that's being lost here.*

vii. *Sundlun*

737. Counsel turned next to *Sundlun* and to the following observations therein:

> "*The critical phrase in the charter is 'beneficial ownership'. What does it mean? Defendants seem to say that in common parlance it implies a trust type of relationship, that it means an equitable, as distinct from mere legal ownership, that it includes a right to income from property, to the proceeds from its sale and so on. Broadly speaking, it does convey all of this, but nothing has been called to my attention which ascribes to 'beneficial ownership' a universal meaning.*"

738. After counsel for Teva read these lines aloud, the following exchange occurred between him and Mr Chandler:

Counsel:	*You'd accept that?*
Mr Chandler:	*I accept that Chancellor Duffy said that.*
Counsel:	*...*[B]*ut you would accept the principle he says, that there is nothing in Delaware law which ascribes to it a universal meaning?*
Mr Chandler:	*There's probably no universal understanding or meaning.*
Counsel:	*And some people use it in the sense in which it was used in* Buechner*, that the stockholders have an equitable interest in the assets?*
Mr Chandler:	*Yes.*
Counsel:	(quoting from the judgment of Chancellor Duffy in *Sundlun*) "*It is, rather, a phrase of art which implies certain relationships and attributes but which requires particularization before its meaning can be precisely determined*." *You see that?*
Mr Chandler:	*Yes.*

viii. *Aronson*

739. Counsel for Teva turned next to the *Aronson* case, a decision of the Delaware Supreme Court concerning derivative rights in which the court observed (at 811) that (i) "*A cardinal precept of the General Corporation Law of the State of Delaware is that directors, rather than shareholders, manage the business and affairs of the corporation*", (ii) "*The business and affairs of a corporation organized under this chapter shall be managed by or under the direction of a board of directors except as may be otherwise provided in the chapter*", and (iii) "*The existence and exercise of this power carries with it certain fundamental fiduciary obligations to the corporation and its shareholders*".

740. In response to a series of questions, Mr Chandler (i) agreed to the foregoing, and to the following propositions of counsel, *viz.* (ii) (a) that what was in issue in *Aronson* was "*whether the court should intervene when directors make what's called a managerial decision where they have a margin of discretion*", (b) that what the court states is that (I) the "*principle of separateness which recognises this is protected by allowing a derivative action if the directors act in breach of fiduciary duty*" and (II) "*the derivative action was a development of the Court of Equity taking into account corporate separateness*".

ix. *Anadarko*

741. Counsel for Teva turned next to the *Anadarko* case and to the observation therein that "*It is a basic principle of Delaware General Corporation Law that directors are subject to the fundamental fiduciary duties.... Specifically, directors cannot stand on both sides of the transaction*", at which point the following exchange occurred between counsel and Mr Chandler:

Counsel:	*Can I just stop there for a moment? Directors of a subsidiary, you've said they owe fiduciary duties to the corporation. They also owe duties under the Delaware Code, isn't that correct? Directors have responsibilities?*
Mr Chandler:	*Directors have responsibilities under the Delaware Code, yes.*
Counsel:	...[C]*ould you just describe, in general terms, what those responsibilities are?*
Mr Chandler:	...[I]*t's set out in section, among others, 141 sets out that it is the obligation or responsibility of the directors to direct and manage the affairs of the company.*
Counsel:	*And where there's a subsidiary, that's what they're obliged to do by law?*
Mr Chandler:	*Whether it's a subsidiary or a parent, the directors of either have that same obligation.*
Counsel:	...[T]*hat is an obligation that would reside also with the directors of BMS Pharma, isn't that correct?*
Mr Chandler:	*Correct.*
Counsel:	*And you would expect responsible directors and lawyers to comply with that obligation..?*
Mr Chandler:	*Yes, I would.*
Counsel:	...[D]*id you make any enquiries as to whether they had complied with that obligation?*
Mr Chandler:	*....Everything I saw and read indicated that they had complied with their fiduciary duties....I saw nothing that caused me to doubt that.*
Counsel:	*So, they acted as a Board of Directors discharging their duties to BMS Pharma?*
Mr Chandler:	*To BMS Co.*
Counsel:	*To BMS Pharma..?*
Mr Chandler:	*Oh, to BMS Pharma? Yes.*

742. Counsel for Teva then referred Mr Chandler to an observation, at p.1176 of the judgment, The observation in question being that "*The concept of 'beneficial ownership' of stock, though somewhat inexact, is contextually defined, and has become a term of art for purposes of establishing fiduciary duties under Delaware law.*" Counsel also turned to:

(i) the observation in *Anadarko* (at 1176) that:

> "*As applied in this case, beneficial ownership contemplates a separation of legal and equitable ownership. Under this concept, the equitable or beneficial owner possesses an economic interest in the subject property*",

at which point the following exchange occurred between counsel and Mr Chandler:

Counsel:	*There again the term "*equitable ownership*" is used by...the Supreme Court of Delaware, to mean an economic interest, isn't that correct*?
Mr Chandler:	It subsumes that.

(ii) the observation therein (at 1177) that:

> "*In order for a trust relationship to exist there must be evidence of an intention on the part of the grantor to separate legal and equitable title to the subject of the trust*",

at which point the following exchange occurred between counsel and Mr Chandler:

Counsel:	*You'd agree with that principle, I take it?*
Mr Chandler:	*Yes.*

x. *Wallace*

743. Counsel for Teva turned next to the *Wallace* case and to the observations therein (at 1183 and 1184) that:

> "*In order to state a cognizable claim to pierce the corporate veil of the General Partner, plaintiffs must allege facts that, if taken as true, demonstrate the Officers' and/or the Parents' complete domination and control of the General Partner. The degree of control required to pierce the veil is 'exclusive domination and control ... to the point that* [the General Partner] *no longer ha*[s] *legal or independent significance of* [its] *own.' Piercing the corporate veil under the alter ego theory 'requires that the corporate structure cause fraud or similar injustice.' Effectively, the corporation must be a sham and exist for no other purpose than as a vehicle for fraud.*"

744. Mr Chandler acknowledged that this was a correct statement of Delaware law.

xi. *Mangano*

745. Counsel for Teva turned next to the *Mangano* case and to the observations therein (at 8) that:

> *"This case turns on the meaning of beneficial interest. Although 'beneficial interest' is a term laden with ambiguity... a contract to be interpreted under state law – it at least implies the existence of some enforceable right or benefit. There is, accordingly, nothing ambiguous about whether Mangano maintains a beneficial interest in the shares.*"

746. At this juncture the following exchange occurred between counsel for Teva and Mr Chandler:

Counsel:	*That is, again, saying that in Delaware law* "beneficial interest" *is a term laden with ambiguity and at least implies the existence of some enforceable right or benefit. You'd agree with that?*
Mr Chandler:	*It can be ambiguous in some instances. In others, it can be clear....It depends on the circumstances....*
Counsel:	*But you'd agree with the principle as stated here?*
Mr Chandler:	*I wouldn't disagree with it.*
Counsel:	*....And it can be used to express an entitlement to enforce some right or benefit?*
Mr Chandler:	"*It*" *being beneficial ownership?*
Counsel:	*Yes. The term here:* "'Beneficial interest' is a term laden with ambiguity... it at least implies the existence of some enforceable right or benefit."
Mr Chandler:	*Correct.*
Counsel:	*And you would distinguish between "beneficial interest" used in that sense and used in the sense of having an equitable ownership of an asset, isn't that correct? That's what it's saying here?*
Mr Chandler:	*Yes.*

xii. *Manichaean Capital*

747. Counsel for Teva turned next to *Manichaean Capital*, a recent judgment of the Delaware Court of Chancery. There, the company's former stockholders, as judgment creditors, brought action against the acquirer of a company and its affiliated entities, seeking to enforce a charging order and obtain payment of an appraisal judgment. In the course of his judgment, Slights VC observed (at 713) that "*Delaware embraces and will protect 'corporate separateness'"* (a proposition with which Mr Chandler agreed) and also that:

> "*The natural starting place when reviewing a claim for reverse veil-piercing are the traditional factors Delaware courts consider when reviewing a traditional veil-piercing claim—the so-called 'alter ego' factors that include insolvency, undercapitalization, commingling of corporate and personal funds, the absence of corporate formalities, and whether the subsidiary is simply a facade for the owner.*"

748. At this juncture the following exchange occurred between counsel for Teva and Mr Chandler:

Counsel:	*Those are the factors.*
Mr Chandler:	*Yes.*
Counsel:	*And do any of those factors apply here?*
Mr Chandler:	*Not to my knowledge.*
Counsel:	"The court should then ask whether the owner is utilizing the corporate form to perpetuate fraud or an injustice." *That's not the position here?*
Mr Chandler:	*No.*
Counsel:	"This inquiry should focus on additional factors, including '(1) the degree to which allowing a reverse pierce would impair the legitimate expectations of any adversely affected shareholders'..."...[t]*hen halfway down the page, (2)...* "The degree to which the corporate entity whose disregard is sought has exercised dominion and control over the insider... (3) the degree to which the injury alleged by the person seeking a reverse pierce is related to the corporate entity's dominion and control of the

insider." *And various factors. Now, one of the concerns that is expressed in these cases is ensuring that the corporate form doesn't itself perpetuate fraud. And if you see a subsidiary with assets, in the normal way you will believe that those assets are going to be available to the creditors, isn't that correct, in the event of an insolvency, in the normal way?*

Mr Chandler: *Yes.*

Counsel: *Yeah. And if a parent company that directs a subsidiary in respect of a particular asset could, in the event of an insolvency, say 'We own that beneficial asset and here are two e-mails that set out our policy in respect of it', you might think that that might effect a fraud on the creditors, isn't that correct?*

Mr Chandler: *It might....*[T]*he bankruptcy judge would have to decide whether to give credit to that, those e-mails and other facts, to decide whether or not they had demonstrated a legitimate and good faith ownership interest in the asset. But, again, it's beyond my expertise.*

Counsel: *Well, you offered some view on this to the Court in Finland....*[W]*hen you were asked by the chief judge what was the position, you did say that...you had no idea how a bankruptcy court would treat that....*[but] *you nevertheless went on and offered a view: "*My view is that a Delaware Court probably would tend to not believe the testimony that was suddenly invented on the day of the bankruptcy.*" You see that?*

Mr Chandler: *Yes, I do. That was because of the way the judge in that case framed the hypothetical to me....*[H]*e said 'Imagine that on the day that they're in bankruptcy court someone suddenly gets up on the stand and says 'We've got a beneficial interest and we always intended that', would that be enough?' And I said not likely; you'd have to have other facts and circumstances.*

Counsel: *And if they produced two e-mails of the ones that we looked at here of 19th and 24th October, I'd say the bankruptcy judge would similarly say 'This is no evidence of beneficial ownership', isn't that correct?*

Mr Chandler: *I don't agree with that.*

Counsel: *....You did say to the court in Finland that everything depended on the facts, isn't that right?*

Mr Chandler: *I think I said that, yes.*

Counsel: *And could you point out to me where, in your report here, that's stated?*

Mr Chandler: *I don't think it's stated in that way*.

11. Mr Chandler's Second Report and the Assignments

749. Counsel noted that Mr Chandler's second report is dated 13th May 2022 and elicited Mr Chandler's agreement to the following facts through a series of questions:

(i) he was aware at this stage that the assignments had been made;
(ii) he was aware that there had been an assignment from the inventors to BMS Pharma;
(iii) none of this is mentioned expressly in his report;
(iv) he thought that he had seen the manual prior to his second report;
(v) this was a manual which set out an intention on the part of BMS Pharma in respect of patent applications where the provisional filing had predated 1st October 2001;

(vi) it contemplated that if a provisional filing had been made prior to 1st October 2001, the applicant was to be BMS Pharma;

(vii) he had seen in Judge Holland's statement the reference to the extensive search for an assignment;

(viii) he did not ask whether any further searches had been carried out to find an assignment for 2001 and 2002;

(ix) the significance of an assignment is that it would probably involve an assignment of an interest from one of the companies to the other;

(x) it was potentially important in terms of what he was offering an opinion on, "[b]*ut it seemed to me that it would only strengthen and bolster the opinion that I was giving*", an observation which prompted the following exchange between counsel and Mr Chandler:

> Counsel: ....[I]*f it was an assignment in 2002 from Pharma to BMS, how would that bolster your opinion?*
>
> Mr Chandler: *Because it shows me that BMS Co really was the equitable owner of that and that's why they could compel the subsidiary to convey it by an assignment. The same as when they did it later; that's further evidence that they were compiling with the directions they were receiving from BMS Co.*
>
> Counsel: *So, an assignment, even without you seeing it, would reinforce your view that BMS already had the beneficial ownership?*
>
> Mr Chandler: *Yes. If it was an assignment to BMS Co, it further strengthens my view that that's because BMS Co was the beneficial owner and could compel the titleholder to assign it. Now, if they were assigning it to some other entity, some third party, that would cut against my opinion.*

(xi) following on from the foregoing, when he heard about the assignment of 2007 and he learned that it was to BMS Co., he considered "*that helps me*";

(xii) he did not believe there to be any reference to the 2007 assignment in his second report;

(xii) in terms of the substance of that assignment, the following exchange took place between counsel and Mr Chandler:

> [Substance of Assignment]
>
> Counsel: ...[T]*his was an assignment of the entire right, isn't that right, and interest? ....*
>
> Mr Chandler: *It's like a quick claim deed, you're giving whatever you have.*
>
> Counsel: *No...if you convey the entire right and interest, those words suggest that what is being conveyed is all rights in respect of it, isn't that correct?*
>
> Mr Chandler: *It's all rights that you possess, if you don't....possess all the rights you cannot convey them....*

Counsel: ...[A] *conveyance of the entire right and interest is, in terms of the terminology, a conveyance of the full and beneficial ownership..?*

Mr Chandler: *Not necessarily. It depends on the circumstances. Most of the time practitioners will use those terms to make sure that there's nothing left but they often use them even though it it's over-encompassing, it encompasses more than what the party actually owns. That's what I use the reference to a quick claim deed, it's the same concept. I execute a quick claim deed because I'm not sure whether I own all of the interest in the real property but whatever I own I'm deeding it to the other party. That's how I view these assignments....*

Counsel: *So, the words "*entire right and interest*", you don't regard them as being words which...convey all rights, legal and beneficial?*

Mr Chandler: *They do convey that....But that only means you have to look to what they actually possess.*

Counsel: *...But if somebody uses those, they are conveying that they do own the entire right and interest..?*

Mr Chandler: *No. They may or they may not.*

Counsel: *No, they are conveying they do,* [but that] *as a matter of fact they may or may not have the full title interest?*

Mr Chandler: *Correct.*

[Filing at Patent Office]

Counsel: *....And that is a statement to the word* [*sic* – 'world'?] *and that assignment, as you know, was filed in the Patent Office?*

Mr Chandler: *Yes....*

Counsel: ...[A]*n assignment registered in a public register is intended to convey a legal position to the public..?*

Mr Chandler: *I would assume so.*

Counsel: *....And it's a serious matter to register a document that misconveys what has occurred..?*

Mr Chandler: *I would assume so.*

Counsel: *And you would not expect an entity of the reputation of BMS Company to do anything like that?*

Mr Chandler: *Course not.*

750. Counsel for Teva turned next to the *Hollinger* decision, noting that (and Mr Chandler agreed with this) he had advanced the case in support of the proposition that corporate formalities would be set aside (in the present case). Asked if it was his evidence to the court "*that despite all of the cases we have seen...you are telling the court that corporate separateness is a formality?*", Mr Chandler stated, among other matters, as follows:

> "*No, it's not a formality....*[A]*s I said earlier....I don't believe that anything that I'm advancing here in the way of a legal opinion about Delaware law requires the Court to set aside the formalities here or to disrespect the integrity or the dignity of any of the entities. You can find that a parent is the beneficial owner of assets in its subsidiary without disrespecting the formality of separation between those entities. That's the point that I think is being lost....*[Corporate separateness is] *a principle of Delaware corporate law. But Delaware courts in the Court of Chancery will, at times, not allow that fundamental principle to impair or impinge upon the fundamental rights or the fundamental operation of a statute like 271 or 220. They will say, 'yes, these companies are independent but for the practical purpose of applying this statute, 271 or 220, I'm going to act as though the assets of one were actually controlled by the other.' It's a very practical solution that the court engages.*"

751. Counsel noted that in the *Hollinger* case, Hollinger Inc., which was the ultimate parent, sought to rely on §271 gave it that right. However, Hollinger International, which was an intermediate subsidiary, said in effect 'Section 271 does not apply because we are not selling the assets of a subsidiary, we are selling the assets of a subsidiary of a subsidiary of a subsidiary', and that the corporate veil could not be pierced. Strine VC in his judgment said, in effect, 'it is not as simple as that because I have to construe §271 and divine whether it was the legislature's intention to give a restrictive reading to §271 or a purposive reading'. So he interpreted §271 and chose not to decide whether Hollinger International's technical statutory defence had merit. Following this summary of *Hollinger*, the following exchange ensued between counsel for Teva and Mr Chandler:

Counsel:	*So, he doesn't decide the issue...?*
Mr Chandler:	*He doesn't decide that technical issue....*
Counsel:	*But that's the issue which you said was the critical issue?*
Mr Chandler:	*What I was said was that his reasoning was the critical point of his opinion that led to his conclusion that 271 wasn't triggered because he effectively disregarded the intervening corporate entities and treated the assets of the ultimate entity at the end of the chain, Telegraph, as though its assets were actually part of International's.*
Counsel:	*....He explicitly says he doesn't decide that issue?*
Mr Chandler:	*He doesn't decide it but he reasons all the way through it....*
Counsel:	*So, it's not pivotal to the outcome in the case?*
Mr Chandler:	*It's pivotal to the reasoning that he used to conclude in his own mind why 271 didn't apply....*
Counsel:	...[J]*udges often say I won't decide that issue, I will make an assumption without deciding it. Even if it was decided in this particular case the plaintiff doesn't succeed. So, you don't decide the issue and not deciding the issue means the same in Ireland as...in the US...you have not decided it..?*
Mr Chandler:	*He is not deciding it....*
Counsel:	...[W]*hy didn't you tell the Court that, that he didn't decide it?*
Mr Chandler:	*Because to me the more important part is how he reasoned through the process of reaching that conclusion, even though he didn't have to decide it and could just assume it and move on, and because that was what later led the legislature to make the amendment they made.*

Counsel: *But he reasoned both sides of it. He set out the arguments of both sides. He...*['said''] *I won't decide that. In Delaware does that amount to a precedent?*

Mr Chandler: *It does because that's the way a Court of Equity works and the judges in the Court of Equity that I was part of reason through things like this and give both sides of the argument and it's not unusual for us to say, you know, I don't really need to decide this....*

Counsel: *....So, if you don't decide it because you don't have to do it's not a precedent?*

Mr Chandler: *It's not a precedent that you can cite in that sense. It is a precedent in the sense that the legislature could look at this, and they did, and say we agree with the logic and the reasoning of this opinion*.

Counsel: ...[T]*hat decision is central to your second report and to Mr. Holland's report?*

Mr Chandler: *It is....*

Counsel: *....And he decided it on the basis that this was not all or substantially all of Hollinger International's assets?*

Mr Chandler: *Correct.*

Counsel: *So, that on any interpretation, Section 271 was not triggered. That's what the case stands for. Section 271 was not triggered....That's what the case stands for?* [I believe what counsel meant with this last question is that this is what *Hollinger* stands for in precedential terms].

Mr Chandler: *That's correct.*

13. *Hologic*

752. Counsel turned lastly to the decision in *Hologic*. There, Hologic was seeking an injunction against Minerva because Minerva was allegedly infringing its patent rights and the US District Court found that (i) Hologic had equitable ownership interest in the patent and (ii) under federal law that gave it the right in standing to seek an injunction. So, the court rejected Minerva's effort to have the case dismissed. A brief exchange occurred between counsel and Mr Chandler concerning the exact import of the case:

Counsel: *What she* [Robinson J.] *decided was...if you go to the last pa*ge... "Under these circumstances...Hologic has established its equitable standing to pursue injunctive relief." *That was what was found?*

Mr Chandler: *Well, she found that Hologic had equitable ownership interest in the patent and that under federal law that gave it the right in standing to seek an injunction. So, she dismissed Minerva's effort to dismiss the case....*

Counsel: *But the basis of her finding and the finding we [sic?] she made is that Hologic had equitable standing to pursue relief and the relief it was claiming was....an injunction?*

Mr Chandler: *The relief it was seeking was an injunction...a form of equitable relief....*[U]*nder federal law if you own the equitable interest in the patent you can see equitable relief if you want to seek legal relief you have to have the legal title to it. So, Judge Robinson was finding they have equitable ownership rights that gives them standing to seek equitable relief.*

Counsel: *This was a decision on federal law..?*

Mr Chandler: *The standing part was....The equitable ownership interest...that's federal law I guess but it was also consistent with Delaware law. There's no inconsistency between federal law and Delaware law over how to find an equitable or beneficial interest....*

Counsel: [Mr Steele] *was of the view that nothing in this decision was relevant to the facts that arise in this case....And I suggest to you that he was correct..?*

Mr Chandler: *I believe he believes he was correct. I don't agree with him. I think it's actually very informative and instructive....*

Counsel: *Just to go back to that second statement again. You identify in paragraph 25, with reference to* Hologic*, that the finding was that the boundaries between the corporations had been breached, isn't that correct?*

[I believe this is a reference to para.25 and footnote 6, where Mr Chandler states as follows:

(i) in para.25:

> "*With these facts in mind,* Hologic, Inc. v. Minerva Surgical, Inc., *163 F. Supp. 3d 118 (D. Del. 2016), is instructive. In* Hologic, *the court echoed the general principles articulated in* Digitech, *but went on to conclude that a parent company had equitable standing with respect to its subsidiary's patents. Id. at 122. The court explained the 'mere fact' of stock ownership or of a corporate relationship does not establish standing, but the record in that case demonstrated 'that boundaries between the corporations at bar ha[d] been breached' such that the parent had equitable title to the patents and, accordingly, equitable standing.* Id[6]",

and

(ii) in footnote 6:

> "*Quoting* Top Victory Elecs. v. Hitachi Ltd., *2010 WL 4722482, at *3 (N.D. Cal. Nov. 15, 2010) ('While the Federal Circuit has been clear that ownership, assignment, or an exclusive license are required for legal remedies, it has indicated that in some circumstances an equitable owner without legal title may pursue equitable remedies. This Court has held that even if the companies are closely operated and the parent purports to act on behalf of the subsidiary, a parent does not have standing in a suit involving patents held by a subsidiary without a showing that boundaries between the corporations have been breached.' (citations omitted))*."]

Mr Chandler: *Yes. Those are...the exact words that Judge Robinson used.*

Counsel: *And I take it you would agree that where a subsidiary exists, has accounts, has directors and officers, is part of a wider group and those directors and officers comply with their duties, that does not involve a breaching of the boundaries?*

Mr Chandler: *No. There were other things that I think Judge Robinson was referring to when she said that.*

D. Re-Examination

1. *Hologic*

753. Counsel for BMS started his re-examination where counsel for Teva had left off, bringing Mr Chandler to the judgment of Robinson J. in *Hologic* and, in particular, to her observation (p. 112 of judgment), immediately after the reference to *Top Victory* and the reference therein to boundaries between the corporations having been breached, that:

> "*More specifically, the record reflects that, at the time the original complaint and the motion for preliminary relief were filed, Cytyc owned the patents-in- suit and Hologic owned and* '*exercised...complete control over Cytyc,*' *including control over all of Cytyc's business decisions and Cytyc's patent enforcement, assignment, and licensing policies*",
>
> with Robinson J. then concluding as follows:
>
> "*According to Hologic,* '*because of the structure of this corporate relationship and Hologic's complete control over Cytyc's patent licensing and enforcement policies, Hologic has had control over the Patents-in-Suit, and has enjoyed exclusive rights thereunder*'."

754. Counsel for BMS then put it to Mr Chandler that this was the basis on which the court had made its finding, at which point the following exchange occurred between Mr Chandler and counsel:

Mr Chandler:	*It is and that's why I think the case is useful or helpful....*[S]*he's* [*i.e.* Robinson J. is] *doing the very thing that I'm doing here which is applying these facts and circumstances about the control of the parent over these assets to reach the same conclusion that I'm reaching, which is that...the parent corporation...had the equitable right to enforce....So, yes, that's what I think is the more important part of her reasoning and why...that case is instructive here. It also is instructive...because she doesn't mention anywhere that there was some...written assignment necessary for her to reach that conclusion....The third reason...why...it's helpful...is she's a federal judge but there's nothing inconsistent with Delaware law in what she's doing....It's totally consistent with how a Delaware judge would go about doing the same analysis.*
Counsel:	*Judge Robinson doesn't record that there's a requirement for iniquity or unfairness..?*
Mr Chandler:	*No, she's looking at the circumstances of the relationship between the parent and the subsidiary, that's what she's looking at, not looking for some unfairness or iniquity.*
Counsel:	*And she doesn't refer to the interests of creditors....affecting a finding of that nature?*
Mr Chandler:	*No, that has no bearing on it at this stage.*

755. Counsel for BMS then brought Mr Chandler to the email of Ms Leung a few six weeks before the BMS Pharma acquisition closed, concerning who would be its directors and officers once acquired. Counsel then asked Mr Chandler whether insofar as his opinions are concerned (*i.e.* the conclusions that he had reached by reference to *Hologic*), the said email supported the opinion that Mr Chandler had formed or undermined it. Mr Chandler responded that it supported it, explaining in the following terms why this was so:

> "[I]*t indicates that that was the purpose or the intention all along was to set this up so*

that BMS Co would control the assets that they were acquiring and they would want to protect those assets naturally by installing their own people in these offices and positions, so that they could carry out their instructions directions on how to treat the assets. So, I view it as supportive, not undermining the opinion that I've given."

2. Equitable Interest of BMS

756. Counsel for BMS noted that in the course of cross-examination counsel for Teva, when he was asking about what is it that happened in the present case (the BMS case) that yielded an equitable interest to BMS Co drew Mr Chandler's attention to the distinction that Mr. Steele drew between beneficial economic interest or equitable economic interest versus ownership. Counsel then asked whether there was anything in the judgment in *Hologic* to suggest that Robinson J. had such a distinction in mind when identifying, by reference to *Digitech*, what the interest was that she had identified? To this, Mr Chandler responded that he had not seen anything in Judge Robinson's opinion that made or drew that distinction. "*I saw her applying typical analysis of, do these facts and circumstances demonstrate that the parent was exercising an ownership interest, a beneficial ownership interest over this interest, the patent in dispute there?*"

3. *Hollinger*

757. Counsel for BMS noted that in the consideration of *Hollinger* it had been suggested that Mr Chandler had not referred in his witness statement to the fact that Strine VC did not decide the question that counsel for Teva was asking him about and brought Mr Chandler to para.12 of his second statement where Mr Chandler, under the heading "*The Hollinger Case*" refers precisely to this fact, stating:

"*In declining to grant an injunction, the court chose 'not to decide whether* [Hollinger] *International's technical statutory defense ha*[d] *merit' and instead '*treat[ed] the *Telegraph* Group as if it were directly owned by [Hollinger] International,' *thereby setting aside the levels of corporate separateness in the 'chain' for purposes if its analysis...*".

758. In a later question concerning *Hollinger*, counsel for BMS put it to Mr Chandler that Robinson J., in *Hologic* did not refer to or place any emphasis upon the fact that the wholly-owned subsidiary's Board had or had not complied with or otherwise observed any legal obligation. Mr Chandler confirmed that this was so: "[S]*he did not mention that at all.*"

4. Agreement with Judge Holland

759. Counsel had Mr Chandler affirm that he agreed with and adopted Judge Holland's statement on Delaware law the analysis set out in his report, Mr Chandler stating in this regard:

"[N]*ot only did I agree with him but I've adopted his statement of Delaware law and the analysis that he set out in his expert report. And applying that same analysis to the facts provided by the Golian statement I'm reaching the very same conclusions as Justice Holland reached in his expert report*."

5. Mr Steele's Report

760. In response to questions from counsel for BMS, Mr Chandler confirmed that (i) he did not have sight of Mr Steele's report before he (Mr Chandler) delivered his first witness statement, (ii) when he delivered his second witness statement, having confirmed the position about what Strine VC elected not to decide in *Hollinger*, he proceeded to examine the analysis of Strine VC and what he believed the consequences of that to be, (iii) he had seen Mr Steele deliver a report in another jurisdiction or had sight of a report delivered by Mr Steele from another jurisdiction. (It is not quite

clear to me which of the two Mr Chandler was confirming).

6. Hearsay

761. Counsel for BMS noted that in the course of cross-examination, counsel for Teva had put various propositions to Mr Chandler concerning hearsay evidence and the status of evidence in this case. He then asked Mr Chandler if he was aware "*that on 25th July 2022 in this case, it was accepted that the e-mails he* [counsel for Teva] *was asking you questions about...*[were] *admitted as evidence in this case*", to which Mr Chandler responded that he was aware that they had been admitted.

7. *Danvir Corporation*

762. Counsel for BMS brought Mr Chandler next to the decision in *Danvir Corporation* and the observation in the second-last paragraph thereof by Berger VC that "*From all of the evidence, I conclude that Dominick was attempting to avoid taxes by making gifts of stock during his lifetime that would not take effect until his death. Everyone agrees that Dominick exercised sole and unfettered control over both corporations until the day he died*". Counsel then noted that Mr Chandler had spoken with counsel for Teva on a number of occasions about the importance to Mr. Chandler's evidence of control and asked if this was the type of analysis that Mr Chandler had in mind. Mr Chandler indicated that it was, "[a]*nd that's what a Delaware court would typically look at; the evidence around the degree to which there was control, guidance, instructions and decisions being made on behalf of the subsidiary, or in the subsidiary actually following those directions and commands.*"

8. Receipt of BMS Manual

763. Counsel for BMS lastly put it to Mr Chandler that insofar as he (Mr Chandler) had suggested in his evidence that he may have had the BMS manual before his second witness statement, in fact it was sent to him in May 2023. Mr Chandler confirmed that he believed that this was so.

E. Further Cross-Examination of Mr Chandler Concerning His Instructions

764. In response to a series of questions from counsel for Teva, Mr Chandler confirmed the following: (i) as regards the duties of an expert in giving evidence he thought what he had said was that he did not receive any formal written instructions, but he did receive informal instructions orally, (ii) as regards the substance of those instructions, he was aware that (a) he was required to be fully informed with respect to all of the evidence and the legal issues that he was being asked to opine about, (b) he was required to answer truthfully under oath, in a courtroom, (c) the evidence given should be evidence that would be helpful or useful to the Court in confronting the issues that it is trying to decide, (d) all experts are expected to be independent and disinterested in the matter in which they are asked to opine about, (e) the opinion that the expert is rendering should be that expert's opinion and not someone else's opinion, and (f) he was required to set out the facts and the legal principles or the legal decisions that support the opinion.

765. In response to further questioning (i) Mr Chandler agreed that he did not in his report state any formal or informal instructions that he received with respect to the conduct and role of an expert witness, (ii) did not accept that he did not set out the precise issues that he was asked to opine upon:

> "*I think my statements do state the opinion that I'm giving and the issues that I was asked to opine on. The communications that I had with the lawyers at WilmerHale and at McCann FitzGerald were clear that I was being asked to opine on basically two issues: One being the issue of equitable versus legal title as a matter of Delaware law; and secondly, the relationship of parent and subsidiary corporations under Delaware law and how that would be implicated here in connection with the dispute over the patent that's the object of this lawsuit....Their instructions were you will be asked*

about the separation of ownership under Delaware law between equitable or beneficial owners and legal owners. You will be asked to opine about the relationship between parent and subsidiary corporations. And in the end you'll be ultimately asked about whether or not the parent corporation here, Bristol-Myers Squibb company, held an equitable or beneficial ownership in the patent in issue and whether that would be the view held by courts in Delaware. And that was the issue and the statements that I was asked to respond to by WilmerHale."

766. Mr Chandler's recollection was that these instructions had been given during an oral discussion, with him also being provided in writing "*the information that they had provided to Justice Holland, while he was living, and I had that and I was able to review that before I concluded that I could give the opinion that I ultimately am giving.*"

767. Asked if he had kept a note of the meeting, Mr Chandler indicated that he believed that he or one of his assistants had done so. When he was in Ireland his assistants had checked for some relevant emails and since his return to the United States they had identified some more, which he was willing to provide, stating in this regard that "[T]*here are e-mails that exist between WilmerHale and Shannon German and me that contain documents and information and other expert reports offered by other experts. But I think the actual questions that I was advised I would be asked to opine on were probably expressed to me in telephone calls or Zoom sessions*" and also that:

"[W]*hen we were told to provide written instructions or e-mails that might reflect written instructions...*[his assistants]*, while I was returning to the United States, did a very quick search trying to find anything that would respond to your enquiry and they forwarded, on short notice, responsive e-mails that they thought might be the e-mails that would be responsive to your question…. But since I've been back we've been able to do a more fulsome search and we've located more e-mails which I would be more than glad to turn over to if it's consistent with Irish law and if my counsel tells me that it isn't privileged, but we are ready to do that.*"

768. Counsel for Teva expressed no interest in these other documents. He asked Mr Chandler whether he was aware that (i) one of the matters that an expert witness is required to be in a position to confirm is the precise facts, instructions and issues on which he has been asked to advise, and (ii) that therefore it is important to have a written record of those, so that they can be verified. Mr Chandler agreed with both propositions.

769. Counsel then proceeded to question Mr Chandler by reference to the documents provided following the quick search done by Mr Chandler's assistants as he was returning to the United States and not by reference to the fuller suite of documents that had been unearthed after Mr Chandler had returned to the United States. I do not believe that it greatly advanced what was already known about the nature and substance of the instructions received.

770. After Judge Holland's death, an email was sent to Mr Chandler asking if he would be able to assist BMS as an expert witness. Reference was made in this email to Judge Holland having provided "*a superb opinion on the issue which we have deployed in several patent litigations*" and it seemed to be intimated by counsel that what was being sought of Mr Chandler was a like opinion. I do not myself see how this could be read into what seemed to me to be a perfectly innocuous email but in any event the following exchange ensued:

Counsel:	*What did you understand by that instruction?*
Mr Chandler:	*I didn't understand it as an instruction* [it patently is not an instruction] *I just saw it as a comment by* [the attorney]*that...*[Judge Holland] *had already provided them with an excellent opinion.*
Counsel:	...[W]*hat did you understand it then in terms of a statement, what*

was being conveyed to you?

Mr Chandler: *It was conveying to me that they appreciated the help that Justice Holland had offered to them up to that time and they were hopeful that I could also help them as well.*

Counsel: *And help them by coming to a similar conclusion, isn't that correct?*

Mr Chandler: *Well, they may have hoped that, but I come to my own conclusions...and I'm not influenced by the fact that a lawyer at WilmerHale may have thought that an opinion by my colleague was excellent or superb or anything else. I come to my own opinions and those are my opinions, not someone else's.*

771. It would be fair to say that counsel continued to intimate that by providing an opinion which adopted another opinion, Mr Chandler had failed to give his own independent opinion. This eventually drew the following response:

> "*I was...giving my own independent opinion. It just so happened that it was consistent with Justice Holland's....*[W]*hat you're trying to insinuate...is that somehow my opinion is parroting Justice Holland''s opinion and is not my own opinion....I do not give an opinion based on what someone else has said or testified to. And I would never...repeat an opinion simply because someone else expressed it....*[T]*he fact that Justice Holland expressed an opinion here that I agree with, means only that I agree with it. But I didn't always agree with Justice Holland....I do not appreciate your suggestion that I somehow cannot make up my own mind and that I'm...beholden to Justice Holland and would express his opinion as my own*."

772. Counsel maintained that he was simply "*exploring with you something that is, by any standards, highly unusual, that instead of setting out your own opinion, that you repeatedly refer not just in this opinion but in your evidence to agreeing with Justice Holland and in fact telling an Irish court what Mr. Justice Holland thought or would have done*". In fact, I believe that counsel for BMS probably caught the truth of matters best when I asked him during his closing submissions about the adoption by a live witness of a report by a dead witness, and he said as follows:

Judge: *Is there actually a difficulty with adopting somebody else's view if you agree with it?*

Counsel: *No. But, Judge, can I just ask can we deal with this on a human level for a moment? We were delivering witness statements the day - we were obliged to deliver them the day those e-mails that Mr. Chandler provided. And the late Judge Holland had died …'. Now, it wasn't just Ireland, Judge, you saw that from the material, he was asked to help out BMS Co in other jurisdictions. And I can't remember, Judge, on the chronology, but I could be wrong about this, I don't think it's material, but I believe he delivered his first witness statement in Sweden, before here. And what''s interesting, Judge, about that is, when you look at the index to Book 14 - and I'll come to that shortly for a different purpose, Judge - if you look at the dates the witness statements are delivered, his witness statement is dated 12th April, Mr. Steele''s is dated 14th April. So, what was he to do? He was being told - and just to be clear about this, Judge, we'll see when we look at My Friends' witness statements that they do exactly the same thing; they look at material that has already been developed in the case and they are asked to provide their comments on it. And therefore, we didn''t understand how what we were being called out as having done was in some way unique or improper, bearing in mind that it seems that*

material was presented in the same way to My Friends' witnesses.

773. By way of additional observation, there were, it is true, a few occasions in Mr Chandler's oral testimony when he stated his evidence and added in effect that 'I believe Judge Holland would have reached the same conclusion'. He is perfectly entitled to his view as to what the late Judge Holland would or would not have done or believed. For my part, as I listened to Mr Chandler's helpful evidence, I immediately discounted such remarks, heeding only what Mr Chandler had to say in his own right (and what he had to say in his own right was both informed and informative). I paid no heed to whether or not it he thought that the late Judge Holland would have agreed with him. Frankly, if the Teva team thought this trait in Mr Chandler's evidence so objectionable they could simply have stated to Mr Chandler during his cross-examination something along the lines of 'With respect, never mind what Mr Holland might have thought' – there would have been no need to add 'please just tell us what your opinion is' because Mr Chandler, an articulate, eloquent, and impressive witness at no time left me (and could not have left any fair-minded listener) in any doubt as to what his opinion was on any given point.

774. Counsel for Teva also seemed to take objection to the fact that more junior members of the law firm where Mr Chandler works assisted him in what might be styled the 'travaux préparatoires' that preceded his opinion. I have no idea why this is objectionable. I believe that I can take judicial notice that most if not all senior lawyers in every major law firm have people who assist them in their daily endeavours. (Here, almost at the outset of his oral testimony, Mr Chandler had described this assistance in his case to involve "[r]*esearch assistance. I mean, if I needed to look at a case, they'd get me the case. If I asked them to sort of give me, you know, the shorthand version of what a decision was, they would do that. They helped me craft the statements the way associates typically help partners in drafting matters*"). But when a senior lawyer puts her/his signature over an opinion and says that s/he is satisfied to issue that opinion as her/his opinion, then that is her/his opinion. I do not see it as a frailty in Mr Chandler's legal opinion that he did not mention that more junior members of his law firm assisted him in this way. Perhaps a secretary typed up the opinion – should he have named this secretary also? No, because that secretary and those assistants are not the person issuing the opinion, not the person who finally evaluates what is to go into that opinion, not the person who signs the opinion, not the person who is responsible for the opinion, and not the person who is putting her or his reputation on the line when it comes to the substance of that opinion.

775. Counsel for Teva ended this line of questioning with the following exchange between himself and Mr Chandler:

> Counsel: *I have to suggest to you Mr. Chandler, that it is not an appropriate way to approach your duties and role as an expert by accepting instructions of the nature that were provided by WilmerHale directing you in relation to the opinion of Mr Holland as being of great help and then referencing throughout not just your reports but your evidence, the opinion of Mr. Holland as a way of supporting or reinforcing what you were to say to the Court*.
>
> [Three points might be made in this regard:
>
> (1) The reference to Mr Chandler being directed in relation to the opinion of Mr Holland as being of great help is, with respect, without foundation. As stated above, reference was made in an email to Judge Holland having provided "*a superb opinion on the issue which we have deployed in several patent litigations*". To me that is an innocuous statement by a professionally polite lawyer referencing the assistance provided by an expert witness whose death has left his instructing law firm somewhat in the lurch, with that

law firm/lawyer reaching out to Mr Chandler for assistance. As to any hope that law firm entertained that Mr Holland might provide a similar opinion, Mr Chandler was quite clear that "*they may have hoped that, but I come to my own conclusions...and I'm not influenced by the fact that a lawyer at WilmerHale may have thought that an opinion by my colleague was excellent or superb or anything else. I come to my own opinions and those are my opinions, not someone else's.*" I have no doubt that when it comes to an expert witness of Mr Chandler's distinction and professional experience this last-quoted evidence represents the complete and unabashed truth.

(2) As to Mr Chandler's adoption of Mr Holland's report, following the death of the latter, I accept the truth of matters to be as counsel for BMS stated when the matter arose in closing submissions, namely (again):

> Judge: *Is there actually a difficulty with adopting somebody else's view if you agree with it?*
>
> Counsel: *No. But, Judge, can I just ask can we deal with this on a human level for a moment? We were delivering witness statements the day - we were obliged to deliver them the day those e-mails that Mr. Chandler provided. And the late Judge Holland had died that wasn't. Now, it wasn't just Ireland, Judge, you saw that from the material, he was asked to help out BMS Co in other jurisdictions. And I can't remember, Judge, on the chronology, but I could be wrong about this, I don't think it's material, but I believe he delivered his first witness statement in Sweden, before here. And what's interesting, Judge, about that is, when you look at the index to Book 14 - and I'll come to that shortly for a different purpose, Judge - if you look at the dates the witness statements are delivered, his witness statement is dated 12th April, Mr. Steele's is dated 14th April. So, what was he to do? He was being told - and just to be clear about this, Judge, we'll see when we look at My Friends' witness statements that they do exactly the same thing; they look at material that has already been developed in the case and they are*

asked to provide their comments on it. And therefore, we didn't understand how what we were being called out as having done was in some way unique or improper, bearing in mind that it seems that material was presented in the same way to My Friends' witnesses.

(3) As to the occasional reference by Mr Chandler to Mr Holland's opinion in the course of his evidence, I have already given my view on this above: they seemed more in the nature of throwaway comments, I discounted anything that was not Mr Chandler's own (invariably informative) view, and if counsel was vexed by the references to what Mr Holland might have thought he could simply have asked Mr Chandler to limit his observations to what he himself thought (not that there was ever any doubt as to what Mr Chandler himself thought). As to the notion that Mr Chandler made reference to Mr Holland to somehow buttress his own view, counsel seemed to me to have forgotten that he had put this possibility to Mr Chandler in the course of his cross-examination and it had been denied. As considered previously above, in the course of cross-examining Mr Chandler counsel put it to Mr Chandler that it was "[o]*dd for an expert witness to ascribe a view to another person who is not giving evidence and who now, unfortunately, is dead. Why would you do that?*". To this, Mr Chandler responded that he had answered so "[b]*ecause I've read Justice Holland's statements. I agree with him entirely. I just believe that he would hold the same conclusions that I do about this case*." Asked if this last point was "*offered to the Court as some reinforcement of...*[Mr Chandler's] *opinion*", Mr Chandler indicated that "*It's just recognising the reality that, unfortunately, Justice Holland isn't with us and can't give his opinion himself*". All this said, when counsel put to Mr Chandler that "[T]*his is your evidence*", Mr Chandler responded "*Oh, absolutely*", and again stated a minute or two later that "*I've spent 50 years building my reputation and I don't give my reputation away. So, whatever opinion I give, it's going to be my opinion*".]

Mr Chandler: *Well, I happen to disagree with you most emphatically....*
Counsel: *And that it is highly unsatisfactory that you would prepare a report without identifying formal questions that had been put to you and the precise instructions that you were obtaining from WilmerHale? ...*[E]*ven now you haven't been able to produce any written instructions identifying the precise questions or the precise facts disclosed to you by WilmerHale?*

[I admit that I was somewhat surprised by this line of questioning: Mr Chandler adopts Mr Holland's report and that report lists the questions that are required to be answered.]

Mr Chandler: *...I have to disagree again...*[Y]*ou're ignoring the fact that I've already said that we have multiple e-mails exchanged between* [Mr Chandler, his juniors]*...and WilmerHale and McCann FitzGerald, those multiple e-mails would reflect the instructions and the questions and the documents and the information, all of which in aggregate I reviewed and studied and came to my opinion about. All of those are there.*

Counsel: *But...we asked for the instructions and what we were given were the e-mails that I furnished and asked you about?*

Mr Chandler: ...[A]*gain, you want to ignore my earlier answer which was you were given those because on an expedited basis, while I was flying back to the United States,* [Mr Chandler's juniors]*...tried to assemble what they thought you were asking for....*[B]*ut those are not the comprehensive and inclusive list of every e-mail dating back to be November 2020 when this whole matter began. So, if you want those, as I stated earlier, we'll be happy to provide those to McCann FitzGerald and to WilmerHale if they believe it's appropriate and require them under Ireland law, which is not my area of expertise, then they'll be happy and I'll be glad to provide all those to you.*

Counsel: *Okay. I had made that request last week but we'll leave that aside, Mr. Chandler.*

[I cannot but respectfully note that this line of questioning seemed to me to be unfair. Mr Chandler was asked to provide certain documents. His assistants provided some documents on an expedited basis as he returned to the United States. He then unearthed a further series of relevant documents and offered to provide them to Teva if BMS's Irish legal team were satisfied for him to do so. Yet he was criticised only by reference to the expedited documents and without any indication as to whether the later documents were wanted. The grievance of counsel for Teva in this regard seemed to me to suffer a dent in credibility once Mr Chandler offered what further documents were available in terms of written instructions and, at least from what I saw in court (it may be that there was correspondence between the parties that I do not know about) counsel evinced essentially no interest in those further documents.]

776. Counsel for Teva proceeded next to engage in some questions that went beyond why Mr Chandler had come back (to give evidence about instructions and related emails). Counsel for Teva maintained that he was testing Mr Chandler's independence but that was not why Mr Chandler had come back. Once objection was raised by counsel for BMS in this regard, counsel for Teva agreed to cease his further cross-examination.

F. Further Re-Examination

777. Counsel for BMS returned to the 'issue' of the initial email sent by WilmerHale to Mr Chandler in the wake of Mr Holland's death, the following exchange taking place between the two:

Counsel: *You referred on a number of occasions to the unexpected and untimely death of your former colleague, Mr. Justice Holland. Can I just ask you to go back to that first e-mail* [that counsel for Teva]*...asked you about...the one on 21st March 2022. And the very*

first paragraph of that says: "I was shocked and saddened to learn of the sudden passing of your colleague Randy Holland. Do please accept my condolences." *How soon before that e-mail was sent, did Judge Holland die?*

Mr Chandler: *It hadn't even been one week....*

Counsel: *....Was there an urgency in relation to the need for opinions in other jurisdictions as a result of the late Judge Holland's death?*

Mr Chandler: *That was the information that was conveyed to me...that they did need someone soon to take up because there was going to be proceedings in other jurisdictions – Sweden, Finland, Spain, France. And, so, there was some expedition needed and that's why I was able to respond a day later because of that need for some expedition.*

Counsel: *And can I ask you to confirm – it's here in court and you've attached it to your witness statement – that Justice Holland* [in his expert report] *lists the questions that are required to be answered?*

Mr Chandler: *Yes, he does. And that's one of...the first things I turned to...look at.*

21

Some Conclusions

778. What key conclusions might be reached following the consideration in previous chapters of the evidence of Messrs Steele and Chandler? It seems to me that the following might safely be stated.

[1] Delaware law recognises that, as between a parent company and its subsidiary, the latter (including its officers) owes fiduciary duties to the former. One can see this:

(i) in the following exchange between counsel and Mr Steele when Mr Steele was under cross-examination, which exchange commences with counsel reading out previous testimony of Mr Steele:

Counsel: . *... 'So one more question on this topic. If we have a case at hand that we have a parent and a subsidiary, and the parent owns hundred per cent of the subsidiary, can the subsidiary company, which has under its own name patents, and trademarks, and so forth, under the Delaware state law do whatever it wants with those assets, whether they are patents or trademarks, so can they do whatever they desire with them without being feared of any consequences if ever the parent company disagrees with these acts they've been doing?'*

And your answer is:

'They cannot, and as all three, I think, of the expert reports relating to Delaware law make clear, the subsidiary owes fiduciary duties of loyalty and care to the parent. So, they can't... even though they are the legally titled owner of the patent, they can't act in their own interest, it's contrary to the parents, or in anyone else's interest that would be contrary to the parent's.

And I think that's a reference to the principle established in Anadarko*, isn't that right?*

Mr Steele: Anadarko *notwithstanding, that's a correct statement of the law. The only problem is that it says 'its'. I mean, the translation loses some of the language. It should be 'if contrary to the parent's interest.'*

Counsel:	*Sorry, of course. And I understood that.*
Mr Steele:	*You're reading it literally then that's fair, but I just wanted to point that out.*
Counsel:	*Okay. But the point I just want to put to you about this, insofar as Delaware law is concerned with a wholly owned subsidiary, like here Pharma, you have accepted that BMS Co owns the beneficial interest in the patent in question, you have accepted because of corporate control there would be no difficulty issuing an instruction or direction to the subsidiary. And your evidence and your acceptance now is that in fact the subsidiary could do nothing with the patent, or indeed any asset, contrary to an instruction of the interests of the parent, isn't that correct?*
Mr Steele:	*Well, contrary to the best interests of the parent, yes. And as a pragmatic point of view, I try to point out that's not a legal rule. They would do what the parent requested them to do, because it's assumed that they will act in the best interests of the parent. And the parent knows what its best interests would be.*
Judge:	*And if the parent was telling them something that might end up in the creditors being defrauded or whatever... the directors of the subsidiary company would presumably have regard to that fact?*
Mr Steele:	*Yes*.
Judge:	*So, they won't just act on instructions will they, they'll think, well, can I do this, is this right?*
Mr Steele:	*And the important thing, Judge, is that the subsidiary can't act contrary to the parent's best interest. And the parent will make a judgment of what's on, in their best interest.*

(ii) in the following statements by Mr Chandler, when under cross-examination by counsel for Teva: (a) "[A]*s a fiduciary principle, under the Anadarko case, the subsidiaries, directors and executive management must follow the directions and do what's in the best interests of the parent sole stoke holder*", and (b) "[There is a] *principle that Delaware recognises that the directors and officers of the subsidiary owe a fiduciary obligation to the controlling, or the only stockholder, the parent corporation, and that that fiduciary obligation is to, as always, act in the very best interests of the controlling, or the only stockholder, the parent company.*"

[2] those fiduciary duties are such as to confer an ability on the parent to control not just the subsidiary, but the assets that it holds.

[3] here, the exercise of the control aforesaid was such as to constitute BMS Co the beneficial owner of US165 as a matter of Delaware law.

[4] consistent with his testimony in Finland and Sweden, Mr. Steele accepted that BMS Co enjoyed the beneficial interest in US165. This is so important a point to have been made by an expert witness called by Teva that it is worth quoting at some length what Mr Steele stated in his evidence. Thus, the following exchanges occurred between counsel and Mr Steele:

(i) Counsel: *And can I ask you to confirm, did you say on a number of separate occasions to the Court in Finland that BMS Co enjoyed beneficial interest in the patent that we're all discussing in this case?*

Mr Steele: *I did.*

Counsel: *And I take it, Mr. Steele, that when you acknowledge that it had a beneficial interest, you were acknowledging that as an ownership interest in the patent, though you did distinguish it from legal interest, isn't that right?*

Mr Steele: *In part. But actually, as...Judge Robinson's case provides, it's an interest economically that allows, under the context of this case, the parent who doesn't have legal title to the patent to protect its economic rights through equity.*

Counsel: *No, but –*

Mr Steele: *So, it's equitable standing.*

Counsel: *But sorry, Mr. Steele, just to be clear, when you talk about economic rights, you're talking about rights you have as a consequence of beneficial ownership, isn't that correct?*

Mr Steele: *I think that's correct, yes.*

Counsel: *Yes. So, insofar as your evidence is concerned, you accept that BMS Co had beneficial ownership and, therefore, had standing to seek equitable remedies to protect the patent, is that correct?*

Mr Steele: *To protect its economic interest in the patent, yes.*

Counsel: *Well, you see, that's where I just don't understand. And I just want to put it to you, Mr. Steele, neither does Mr. Chandler understand what that evidence is directed towards. Because if the beneficial ownership is in BMS Co, logically it has the right to invoke equity to protect its property interest, isn't that correct?*

Mr Steele: *That is correct.*

Counsel: *And the one remedy it doesn't have, Mr. Steele, is the right to sue for damages at federal law, because it doesn't hold the legal interest?*

Mr Steele: *I'll take that as a question. Yes.*

(ii) Counsel: [counsel again commences with a reference to

Mr Steele's oral testimony in Finland]

> *"The cases talk about equitable interest being protected through equitable claims and equitable relief. I don't think that's disputed by anyone. What the federal cases say, as I read them, is that that equitable owner lacks standing, in other words, cannot bring a lawsuit for money damages..."*

And that's what you've just been referring to now, isn't that right?

Mr Steele: *Correct*.

Counsel: *And you continue:*

> *"...for an infringer of the patent, or any actions taken to damage that economic interest, that's only held as a matter of a beneficiary relationship. That can only be done... all of the remedies in equity (and) law can only be sought by a formally titled owner of the patent."*

And as I understand your evidence there, what you're saying is if you hold both the legal and beneficial interest or ownership in the patent, you can sue for both sets of remedies, but if you only hold the beneficial ownership of the patent, you're limited to equitable relief, isn't that right?

Mr Steele: *That's my understanding, yes.*

Counsel: *Then if you go forward, if you wouldn't mind then, to page – it should, I believe, be page 10 and at the top of the page you're asked a question:*

> *"Now, you said earlier that you agree that a parent can ask or tell the subsidiary to transfer certain assets. Do you know whether in this case such a request or a command was given?"*

And you say, and you've talked to [counsel for Teva]*...about this:*

> *"My recollection of facts is, six years later, there was an actual assignment made formalizing the transfer, but until that time, the only interest that BMS had would*

be equitable ownership of the patent."

Isn't that correct?

Mr Steele: *I said that, yes.*

Counsel: *And that's your language, that's your assessment as an expert in Delaware law that the equitable ownership of the patent was owned by BMS Company, isn't that correct?*

Mr Steele: *Yes.*

Counsel: *Then if you look four paragraphs down:*

"BMS (would) only have the beneficial interest that is sometimes referred to as an equitable title, and not legal title."

And again that remains your evidence, isn't that right?

Mr Steele: *That's correct.*

[5] the relationship between the fiduciary duties of a subsidiary under Delaware law and the entitlement of a parent company to effect control over its subsidiary can be stated in the following terms (the quoted exchange begins with counsel reading out previous testimony of Mr Steele):

Counsel: . *...'So one more question on this topic. If we have a case at hand that we have a parent and a subsidiary, and the parent owns hundred per cent of the subsidiary, can the subsidiary company, which has under its own name patents, and trademarks, and so forth, under the Delaware state law do whatever it wants with those assets, whether they are patents or trademarks, so can they do whatever they desire with them without being feared of any consequences if ever the parent company disagrees with these acts they've been doing?'*

And your answer is:

'They cannot, and as all three, I think, of the expert reports relating to Delaware law make clear, the subsidiary owes fiduciary duties of loyalty and care to the parent. So, they can't... even though they are the legally titled owner of the patent, they

can't act in their own interest, it's contrary to the parents, or in anyone else's interest that would be contrary to the parent's.'

And I think that's a reference to the principle established in Anadarko*, isn't that right?*

Mr Steele: Anadarko *notwithstanding, that's a correct statement of the law. The only problem is that it says 'its'. I mean, the translation loses some of the language. It should be 'if contrary to the parent's interest.'*

Counsel: *Sorry, of course. And I understood that.*

Mr Steele: *You're reading it literally then that's fair, but I just wanted to point that out.*

Counsel: *Okay. But the point I just want to put to you about this, insofar as Delaware law is concerned with a wholly owned subsidiary, like here Pharma, you have accepted that BMS Co owns the beneficial interest in the patent in question, you have accepted because of corporate control there would be no difficulty issuing an instruction or direction to the subsidiary. And your evidence and your acceptance now is that in fact the subsidiary could do nothing with the patent, or indeed any asset, contrary to an instruction of the interests of the parent, isn't that correct?*

Mr Steele: *Well, contrary to the best interests of the parent, yes. And as a pragmatic point of view, I try to point out that's not a legal rule. They would do what the parent requested them to do, because it's assumed that they will act in the best interests of the parent. And the parent knows what its best interests would be.*

[6] the control exercisable by a parent company under Delaware law includes the ability to call on the subsidiary to transfer assets to the parent, Mr. Steele confirming this in the following terms:

Counsel: *You say that the parent can have a right to call for assets, 100% parent, is that correct?*

Mr Steele: *I'm saying that it's highly unlikely, as a practical matter, if the parent called for an asset to be transferred that the subsidiary, given its fiduciary duty, would not agree*.

Counsel: *And the fiduciary duty is something that, if the parent made a call for it, it's likely that the subsidiary would transfer that asset to the parent?*

Mr Steele: *It is likely. Even if the subsidiary might quarrel with the assessment that it's in the best interests of the parent, they more likely than not would do so any way.*

[7] BMS Co's standing as beneficial owner can be described in the following terms:

Counsel: *And just then the final topic I want to come to is just three brief points. You say, as I understand it, in your expert report that when there's a statement made, for*

example at paragraph 30:

> *"I disagree with the following two opinions that Justice Holland offered in his report: First, he opined that 'as a matter of Delaware law, when BMS filed the later patent application in 2002, by virtue of its 100% ownership of its subsidiary BMS Pharma Company, and its stated internal policy as to patent filings, BMS had the unfettered right to call for such subsidiary to assign to BMS the right to claim priority from the earlier filed patent application.'"*

As I understand your evidence in Finland, you actually don't disagree with that proposition, but you do disagree with the proposition that that calling would effectuate the legal transfer, is that a fair summary?

Mr Steele: *That is.*

Counsel: *And then the second point you make is:*

> *"Second, he opined that 'BMS had and has the absolute right to direct the legal title holder of the patent, Bristol-Myers Squibb Pharma Company, to take any and all action regarding the patent that is in the best interest of BMS.'"*

And again if I understand your evidence from Finland, and the exchange we've been having this afternoon, you actually don't disagree with that proposition either, as long as I understand your evidence that that doesn't amount, in law, if I understand the distinction you have you draw, to the vesting immediately of the legal title?

Mr Steele: *That's fair.*

Counsel: *Then at 32 you address:*

> *"Further, the mere possibility for a corporate parent to instruct a subsidiary to assign an asset does not, under the laws of Delaware, equate to an assignment actually carried out."*

And that, again, is a reference to the legal or registered interest, if I understand your evidence, not the fact that the beneficial interest was in BMS Co, isn't that right. Isn't that correct?

Mr Steele: *It doesn't go to whether there was beneficial ownership, it goes to the fact that it wasn't effectuated.*

[8] the exercise of control offers a basis for recognising beneficial ownership in the present case, though such equitable ownership would not arise in every

case where there is a parent-subsidiary relationship, Mr Chandler offering the following views in this regard:

(i)

Counsel: *So, where is the inequity in the parent company holding its assets through a subsidiary, where is the inequity in that?*

Mr Chandler: *So, again I'm going to repeat myself; there's no inequity. But the inequity here in this particular case -- as a general proposition, there's no inequity. Here, the inequity would be you would be depriving the true owner of its ownership rights if you didn't recognise that it had established a relationship with its subsidiary whereby it exercised total control over that subsidiary's asset, the patent in question. And so it determined that it wanted to maintain this division of ownership for business reasons. And all I'm saying is what the inequity would be here is if you failed to recognise that. In many other subsidiary/parent relationships, there wouldn't be any inequity, because the parent may want the legal title and the beneficial title to be residing in the subsidiary. That may be true in lots of cases, I'm sure it is. This is the case that's an exception to that general proposition.*

Counsel: *And where do you glean the evidence that BMS wanted the beneficial ownership, where do you glean that from?*

Mr Chandler: *From all of the evidence that indicates that they controlled the beneficial interest, that they exercised -- they had the legal team that provided directions to Pharma - Pharma didn't have its own legal team - they had the intellectual property lawyers at BMS Co that informed BMS Pharma how to treat the patents, because BMS Pharma didn't have any of those things. They controlled and absolutely determined what was done with that asset. That's what gives them the beneficial ownership right.*

(ii)

Counsel: ...[W]*hat basis does that control, which is a right through a share ownership, result in a transfer of beneficial ownership in an asset?*

Mr Chandler: *So, I think if you're asking me that the sheer ownership of 100% of the stock of BMS Pharma, that doesn't result. I've said that earlier. That doesn't, by itself, constitute a transfer of the beneficial ownership. It would be the other circumstances surrounding the way they dealt with each other, the parent and the subsidiary, and with this particular asset especially and how they organise the relationship. That was all done to make sure that BMS Co maintained and kept the*

beneficial rights of ownership.

Counsel: *Okay. Well, when you say they maintained and kept, when did they get them? To maintain and keep something, you must have it.*

Mr Chandler: *From the very beginning.*

Counsel: *But they didn't have it from the very beginning.*

Mr Chandler: *Well, the minute that they instructed BMS Pharma –*

Counsel: *I see. That's it?*

Counsel (BMS): *Sorry, would you please let the witness answer?*

Counsel (Teva): *I do apologise.*

Mr Chandler: *I mean, they gave instructions. And from the movement they set up - I apologise, you don't like me using the words "set up" – but the minute they began organising Pharma and renaming it BMS Pharma, all of the instructions were coming from BMS Co down to the subsidiary - and all of its employees, by the way, are, as I understand it, BMS Co employees and directors - and they're instructing them how the assets are going to be titled, that the existing patents are going to be titled in the name of Pharma, future patents are going to be, instead, titled in the name of BMS Co. So, the parent is controlling completely how the subsidiary deals with that piece of property. That's the moment in which, you know, to a judge, I would say the relationship from the beginning was one where Bristol-Myers Squibb, the company, was saying 'We're in control, we are the beneficial owner of this asset, you're simply holding the legal title, which we can dip into and take as we wish and do with as with we wish.*

(iii) Counsel: ...[Y]*ou have been talking to* [counsel]*...on a series of different occasions about the importance to your evidence of control. Is that the type of analysis that you have in mind?*

Mr Chandler: *It is. And that's what a Delaware court would typically look at; the evidence around the degree to which there was control, guidance, instructions and decisions being made on behalf of the subsidiary, or in the subsidiary actually following those directions and commands.*

[9] the judgment of Robinson J. in her US District Court decision in *Hologic Inc v. Minerva Surgical Inc* 163 F. Supp. 3d 118 (D.Del. 2016), offers a litmus test against which to gauge the accuracy of Mr Chandler's views as to the due application of equity in the factual matrix presenting in the present case (with Mr Chandler, in the quoted exchange that follows, clearly seeing *Hologic* to offer a solid sense of how a Delaware court would also proceed in this regard):

Counsel: *And insofar as this judgment* [*Hologic*] *is concerned, this is the United States District Court for Delaware. And in that context, can I ask you to confirm to the Court, what happens in the Federal*

Court when the Federal Court is required to consider concepts of Delaware law; does it look for a ruling from the Delaware courts or what is the approach?

Mr Chandler: *Well, there's no federal common law. So, if the Federal Court in Delaware is looking to common law, it would look to the common law of Delaware, particularly if it involves a Delaware corporation, as it did here. So, Judge Robinson would have been doing what any Federal District Court judge in Delaware would do, she would look to Delaware common law to figure out how to determine the question presented. And here, the question presented is exactly like the question presented in this case, in my judgment, which is did Hologic, the parent corporation, possess a beneficial interest in the patent that was held solely in the legal title in the name of its subsidiary, its wholly-owned subsidiary? She looked at it the way a Delaware lawyer and a Delaware judge would look at it, which is what are the indications, the facts and circumstances that would support a finding that the parent company, Hologic, owned the beneficial interest in the patent in dispute? So, she mentioned things such as it had complete control and unfettered control over the patent and how it was used and deployed, whether it was licensed and enforced or assigned, that it made those decisions for its subsidiary, just like BMS Co in this case makes the very same decisions with respect to the patent here. So, Judge Robinson found that because those boundaries - she referred to it as the boundaries of the corporations - had been breached in that way, she found that it was essentially the equitable owner of the patent in question there, and so it gave her the right to say that 'Minerva, your effort to dismiss the case on the grounds that Hologic doesn't own the patent is not going to be granted, Hologic will be allowed to enforce its rights and seek an injunction against Minerva to prevent Minerva from infringing on that patent and the rights that go with that patent to sell or market' - I think it was medical products or something that were in issue here, Your Honour. So, that was her ruling. And to me, it's also sort of noteworthy that Judge Robinson doesn't refer to any kind of written agreement or written assignment as being necessary, she applied the classic test for determining whether or not an equitable interest exists. And that interest is defined under Delaware law exactly as she wrote her opinion.*

[10] Delaware law approaches the issue of equitable ownership in what counsel for BMS refer to in their written submissions as "*a multi-faceted way*" which

has the result that the finding of equitable ownership by a Delaware court would not depend solely on a parent company's ownership of the entirety of a subsidiary company's shares, Mr Chandler testifying as follows in this regard:

> "*In* Digitech *you only had one thing - the fact that the parent owned 100%. And Judge Wright, the Federal judge, said that's not enough to find equitable title. But in Hologic, Judge Robinson had more than that; she had not only the fact of 100% ownership and the fiduciary obligation that the sub, you know, pays to the parent, but she had all the other facts, just like here, to lead her to the finding of the parent was really the equitable and beneficial owner*."

779. In passing, I was a little surprised at the degree of 'surprise' with which Teva greeted Mr Chandler's oral testimony, even as he delivered that testimony, concerning the laws of Delaware and how a Delaware court exercising equitable jurisdiction would adjudicate upon the question of beneficial ownership on the facts of the case presenting before me. Leaving aside that Mr Chandler is a distinguished lawyer and an experienced, retired senior judge whose evidence, as one would instinctively expect of such a seasoned professional, was patently honest, informed, and impressive, it is important to note that, as I have noted previously above, Mr Steele (the Delaware-law witness called by Teva) had already agreed that BMS Co was the equitable owner of US165 under Delaware law, a point that he had previously accepted when giving evidence elsewhere in parallel proceedings to the within proceedings. So I was and remain unsure what the cause of the 'surprise' was concerning Mr Chandler's testimony in this regard. The absence of any basis for surprise in this regard is evidenced by the following brief exchange between counsel for Teva and Mr Chandler:

Counsel:	*You know there's a distinction between setting up a subsidiary and purchasing one, don't you?*
Mr Chandler:	*I think so.*
Counsel:	*Yeah. So, it* [BMS] *purchased. So, we can leave setting up out. What is inequitable?*
Mr Chandler:	*Again, I think your question is begging the real question, which is what are the figures here that a Delaware court would apply to determine whether or not the parent company maintained an equitable and beneficial ownership in the assets of the subsidiary? That's the question. And I've given you my answer about how I concluded and about how Justice Holland concluded and how I think even Chief Justice Steele has concluded that it has a beneficial interest.*
Counsel:	*We'll come to all of that, Mr. Chandler. But we're asking now* [about] *the principle.*

780. Though counsel was of course free to explore the issue of principle, what is unmissable in the above exchange is that both Mr Steele and Mr Chandler were in agreement as to at least one outcome, that being that BMS Co was the equitable owner of US165 under Delaware law. (Mr Steele, the expert witness on Delaware law called by Teva, expressed some reservation as to whether some supervening additional requirement applied under the US Patents Act (a federal measure) could offset what would otherwise be the effect of Delaware law to confer equitable ownership of US 165 on BMS Co. However, the evidence before me shows there to be no such supervening additional requirement.)

VIII. THE SCIENTIFIC EVIDENCE

22

Some Prefatory Observations

1. Introduction

781. Most of the remaining chapters of this judgment are concerned with the scientific evidence that featured in this case. Before I move on to consider that evidence it is useful to deal with some general issues that present in this regard.

782. It will be recalled that in chapter 1, I indicated that that while Teva has made sufficiency and obviousness attacks, in fact the case has become one that is primarily concerned with sufficiency. I noted too that the written closing submissions of BMS state why this is so with (if I might respectfully observe) admirable cogency and in terms which I have adopted and repeat hereafter:

> "*It is said that 652 does not plausibly disclose that apixaban is a factor Xa inhibitor and that it is accordingly insufficient within the meaning of section 58(b) of the Patents Act 1992. It is also said that the claims of the Patent contain no technical advance over the disclosure of WO 00/39131 for the same reason and accordingly that they lack inventive step/are obvious. The allegation of obviousness adds nothing to the case: it is common ground that 131 only encompasses apixaban as part of its Markush formulae and does not disclose a compound with a lactam in the P4 position at all. Consequently, 131 does not disclose apixaban in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. It follows that, if the court determines that 652 also does not render apixaban plausible as having factor Xa inhibitory activity, then the Patent is invalid for insufficiency and obviousness. Conversely, if the court determines that 652 does render apixaban plausible as having factor Xa inhibitory activity, then 652 is sufficient and is not obvious over 131. Consequently* [as I have mentioned above]*...the only question the court has to answer is whether 652 makes apixaban plausible as a factor Xa inhibitor.*"

2. Sufficiency/Plausibility

i. Introduction

783. The first of the matters that I turn to consider in these prefatory observations to the scientific evidence considered in the pages that follow is the law as to sufficiency and plausibility.

ii. Sections 58 and 72

784. Section 58 of the Patents Act, as amended, provides that:

> "*An application for revocation of a patent may be made only on the grounds that...(b) the specification of the patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*".

785. In the United Kingdom, s.72 of the Patents Act 1977, as amended, makes like provision, providing that:

> "*Subject to the following provisions of this Act, the court or the comptroller may by order revoke a patent for an invention...on (but only on) any of the following grounds, that is to say – (c) the specification of the patent does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art*".

786. The effect of s.72 was summarised in the United Kingdom by Kitchin L.J., as he then was, in *Regeneron* v. *Genentech* [2013] EWCA Civ 93. (That was an appeal in two actions concerning the infringement and validity of European patent (UK) No. 1,238,986. Genentech was the proprietor of the patent which related to particular agents called human vascular endothelial growth factor (hVEGF) antagonists for the treatment of noncancerous (non-neoplastic) diseases characterised by excessive blood vessel growth. The appellants were Regeneron Pharmaceuticals Inc, the developer of a product called VEGF-Trap for the treatment of neo-vascular age-related macular degeneration, and Bayer Pharma AG, which wished to sell VEGF-Trap in the United Kingdom. VEGF-Trap was able to bind to VEGF and inhibit its biological activity. Genentech alleged that VEGF-Trap infringed its patent and the appellants counterclaimed for invalidity on grounds of lack of novelty, obviousness and insufficiency. They also sought declarations of non-infringement in respect of VEGF-Trap. It was held by the Court of Appeal that when considering the sufficiency of a patent, an assertion that an invention would work across the scope of the claim had to be plausible or credible. If it was possible to make such a prediction then it could not be said that the claim was insufficient simply because the patentee had not demonstrated that the invention worked in every case. If it was not possible to make such a prediction, or if it was shown that the prediction was wrong, and the invention did not work with substantially all the products or methods falling within the scope of the claim, then the scope of the monopoly would exceed the technical contribution made by the patentee to the art and the claim would be insufficient.)

787. The summary of Kitchin L.J. in *Regeneron* was more recently endorsed by Birss L.J. in *FibroGen Inc.* v. *Akebia Therapeutics Inc.* [2021] EWCA Civ. 1279. That case involved an appeal in (i) revocation proceedings brought by Akebia Therapeutics Inc and Otsuka Pharmaceutical Company Ltd in relation to six patents of which FibroGen, Inc. was the proprietor, and (ii) a cross-claim for threatened infringement brought by Astellas Pharma Inc., the exclusive licensee under the patents. The patents concerned the use of certain enzyme inhibitors, namely hypoxia inducible factor-prolyl hydroxylase inhibitors, for treating anaemia and related conditions. Astellas intended to launch an oral HIF-PHI, roxadustat, in the UK. Akebia had brought the revocation proceedings to clear the path for its own HIF-PHI product, 'vadadustat', and denied that it threatened to infringe. The grounds of invalidity relied on by Akebia were obviousness (including *Agrevo* obviousness) and insufficiency. The Court of Appeal considered the correct approach to undue burden when considering sufficiency of pharmaceutical patent disclosure in claims based on compounds and classes of compounds with a mixture of structural and functional features. In a claim with a functional feature which defined the claimed compounds, or a mix of structural and functional features, the court held, it had to be possible without undue burden, both to identify compounds which satisfied the relevant test, and to find out whether any given compound satisfied the test. However, the court indicated that it was not necessary as a matter of law to establish that the skilled person could identify all or substantially all the compounds which satisfied the test.

788. In his judgment in *FibroGen*, Birss L.J. states as follows (at §§51 and 52):

> "*51. The most up to date general statement of the relevant law of insufficiency, particularly as it relates to claim breadth in this context, is that made by Kitchin L.J. in Regeneron v Genentech in the Court of Appeal at paragraphs [95] to [103]. The whole passage repays careful reading. It is not necessary to set it all out. The fourth principle of the six which Kitchin L.J. identifies relates to inventions defined in general terms and the requirement of a reasonable prediction:*
>
> > *98. Fourth, it is permissible to define an invention using general terms provided the patent discloses a principle of general application in the sense that it can reasonably be expected the invention will work with anything falling within the scope of these terms.*

> *As Lord Hoffmann said in Biogen Inc. v Medeva plc [1997] R.P.C. 1 at pp.48–49 :*
>
> *'If the invention discloses a principle capable of general application, the claims may be in correspondingly general terms. The patentee need not show that he has proved its application in every individual instance. On the other hand, if the claims include a number of discrete methods or products, the patentee must enable the invention to be performed in respect of each of them.Thus if the patent has hit upon a new product which has a beneficial effect but cannot demonstrate that there is a common principle by which that effect will be shared by other products of the same class, he will be entitled to a patent for that product but not for the class, even though some may subsequently turn out to have the same beneficial effect: see May & Baker Ltd v Boots Pure Drug Co. Ltd (1950) 67 R.P.C. 23, 50 . On the other hand, if he has disclosed a beneficial property which is common to the class, he will be entitled to a patent for all products of that class (assuming them to be new) even though he has not himself made more than one or two of them.'*

...

> *52. It may be a matter of taste only but I prefer to refer to this fourth principle as reasonable prediction rather than simply plausibility, however whatever it is called, it is the same principle.*"

iii. Three Types of Insufficiency

789. It is now, if not trite law, certainly well established as a matter of law that one may fall foul of the requirement for sufficiency in three distinct ways:

(i) classical insufficiency

Classical insufficiency arises where the specification fails to give enough information or instruction to the skilled addressee to enable her to put the invention into practice.

(ii) insufficiency across the breadth of the claim

This is often referred to as 'Biogen insufficiency', a reference to the decision of the House of Lords in *Biogen Inc*. v. *Medeva plc* [1997] RPC 1. In these cases the specification fails to provide enough teaching to enable the claim to be carried out across its full breadth. (In *Biogen*, the patent in suit, which related to a DNA sequence coding for hepatitis B virus antigen, claimed priority from an earlier application (Biogen 1). The priority claim was effective only if the claimed invention was supported by matter disclosed in Biogen 1. In an action by the proprietor for infringement of the patent, the defendant counterclaimed for revocation, alleging that the claimed invention was obvious both at the priority date and at the date of the application for the patent in suit, that the patent was not entitled to the priority date of Biogen 1 which did not support the invention claimed, that the claimed invention was not an invention at all, and that the description in the specification of the patent was insufficient. The plaintiff conceded that the claimed invention was obvious at the date

of the application but not at the date of Biogen 1. At first instance the judge found the patent valid and infringed. The Court of Appeal allowed an appeal, holding that Biogen 1 did not support the claimed invention which in any case was obvious at the earlier date, and that the description in the specification was insufficient. The plaintiff appealed to the House of Lords. The House of Lords found the patent to be invalid and dismissed the appeal. Among its findings were that a specification must enable the invention to be performed to the full extent of the monopoly claimed).

(iii) uncertainty insufficiency

Uncertainty insufficiency arises where the scope of the claim is so unclear that one cannot determine over a significant part of it whether what is being done falls within the claim or not.

790. The present case is concerned only with the first type of sufficiency. Because the claim in this case is to a single compound there is no question of breadth of claim. So the question that presents for me is simply whether the claim to that compound is justified, *i.e.* sufficiently described to enable the person skilled in the art to put it into practice. The question arising in determining the sufficiency of that claim is the classical form: Does the specification disclose enough information to enable the skilled addressee to carry out the claim to make the claimed compound?

iv. *AgrEvo*

791. The scope of the claim of a patent must correspond to the technical contribution which the patentee has made in the art. If the scope of the monopoly claim is broader than that contribution, the patent is insufficient. Equally, if the claim is entirely speculative it is insufficient because there is no technical contribution. This has long been recognised in the case-law of the European Patent Office. The requirement for a claim to make a technical contribution not only for the purposes of sufficiency but for the purposes of obviousness was first fully recognised in Case T0939/92 *Triazoles/AGREVO* (ECLI:EP:BA:1995:T093992.19950912).

792. *AgrEvo* is a decision of the European Patent Office's Board of Appeal and is considered to have established the concept of plausibility (though curiously the word 'plausible' does not actually appear in the decision of the Board). In *AgrEvo*, claim 1 of the European patent application was concerned with a range of triazole compounds that were allegedly useful as herbicides. The European Patent Office's Examining Division determined that the scope of the claims did not involve a reasonable generalisation of the examples provided in the description. This was because only tens of compounds were tested for their herbicidal effect whereas the claims extended to millions of compounds. On appeal, the Technical Board of Appeal agreed. Its decision was informed by the principle that the extent of a patent (and hence of the monopoly conferred thereby) should be commensurate with the technical contribution made by a patent to the art. In Europe, inventive step is assessed using what is known as the 'problem-solution' approach. This requires in effect that a solution to an underlying technical problem must be achieved across the whole scope of the claims. In *AgrEvo*, the Technical Board of Appeal essentially decided that because herbicidal effect could only be shown in respect of some of the claimed compounds, inventive step had not been established across the whole breadth of the claim. The effect of the decision was that it must be credible that a technical effect is achieved across the whole breadth of the claims. Perhaps of especial interest are §§2.4.–2.4.2 of the decision of the Technical Board of Appeal, which state as follows:

"2.*4.* *During the oral proceedings the Appellant agued that the only question arising under Article 56 EPC in the present case was whether or not, in the light of the above state of the art, a skilled person would have prepared, or tried to prepare, the claimed compounds....Article 56 did not expressly require, so he submitted, that the subject-matter of a patent application had to solve a technical problem, and that, accordingly, the issue of inventive*

step had to be decided without regard to the solution of any technical problem.

2.4.1 Whilst the Board agrees with the Appellant that the above question is the one which has to be answered under Article 56 EPC, it does not agree with his inference that the existence of a technical problem and its solution, including the problem of proposing alternatives to known activities (e.g. chemical processes) or physical entities (e.g. chemical compounds) is irrelevant to answering this question and so deciding the issue.

2.4.2 The reason for this is, that it has for long been a generally accepted legal principle that the extent of the patent monopoly should correspond to and be justified by the technical contribution to the art (see T409/91...and T435/91)....Now, whereas in both the above decisions this general legal principle was applied in relation to the extent of the patent protection that was justified by reference to the requirements of Articles 83 and 84 EPC, the same legal principle also governs the decision that is required to be made under Article 56 EPC, for everything falling within a valid claim has to be inventive. If this is not the case, the claim must be amended so as to exclude obvious subject-matter in order to justify the monopoly."

793. It may assist to note at this juncture that Arts 56, 83, and 84 of the European Patent Convention are respectively concerned with obviousness, sufficiency and clarity. Thus:

Article 56 ("*Inventive Step*") provides that:

> "*An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. If the state of the art also includes documents within the meaning of Article 54, paragraph 3, these documents shall not be considered in deciding whether there has been an inventive step*."

Article 83 ("*Disclosure of the invention*"): provides that:

> "*The European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*."

Article 84 ("*Claims*") provides that:

> "*The claims shall define the matter for which protection is sought. They shall be clear and concise and be supported by the description*."

v. Classical Insufficiency and Novel Chemical Compounds

794. When it comes to claims for a single compound, a relatively simple justification for the claimed technical effect of a compound may provide a reasonable basis for concluding that the claim is likely to be true. The broader the scope of the claim, the greater the evidential justification required to support it.

795. Classical insufficiency, when applied to claims to novel chemical compounds, requires not merely that (i) a patent identify the compound and, if necessary, how to make it, but also that (ii) it (a) provide a technical reason for doing so and (b) justify the claim that the claimed compound will provide the technical advantage claimed for it. This requirement is often expressed as a need for the specification to make the technical advantage of the claimed compound plausible to the skilled addressee. In other words, does it give the skilled addressee a sufficient reason to think the new compound will work? (As mentioned previously above, plausibility is not a separate statutory

requirement, but an aspect of the requirements for the claim to be either sufficient or not obvious.)

796. The just-described test was referred to with approval by Collins J. in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals* v. *Boehringer Ingelheim Pharma GmbH* [2022] IECA 58, §174, on the basis of the exposition of it by Kitchin L.J. in *Idenix Pharmaceuticals Inc*. v. *Gilead Sciences Inc*. [2016] EWCA Civ. 1089, §114. In *Idenix*, the Court of Appeal held that Idenix's patent for a family of nucleoside analogues for the treatment of various Flaviviridae viruses was invalid for lack of novelty and inventive step and insufficiency. Invalidity for lack of inventive step and insufficiency was based on effectively the same ground: that it was not plausible that substantially all of the claimed compounds would be effective against Flaviviridae viruses. In the course of his judgment in that case, Kitchin L.J., as he then was, observed:

> "[T]*he same approach should be adopted in considering obviousness and whether a technical effect is plausible in the light of the teaching in the specification and the common general knowledge. There must be a real reason for supposing that the claimed invention will indeed have the promised technical effect.*"

797. I note in passing that the facts at play in *Idenix* have a resonance in the context of the present proceedings insofar as the 'standing to sue' points made by Prof. Thomas in the course of his evidence are concerned. Here, a key question before me is whether BMS Co had equitable ownership in US165 at the relevant time. In *Idenix Pharmaceuticals Inc v Gilead Inc and others* [2014] EWHC 3916 the question was whether Gilead had equitable title to the priority document at the relevant time, in circumstances where Idenix contended that the holder of equitable title in a patent did not have standing to sue in the US courts such that equitable title should not be regarded as substantive ownership under US law. Finding against Idenix on this point, the trial judge (Arnold J. observed):

> "*415. ...*[T]*he question of standing to sue for infringement of a granted US patent in the US courts is irrelevant to the issue before this court. I am not concerned with a granted US patent, but with title to an invention at a time when no patent had been granted. Nor am I concerned with the ability of the (equitable) owner to* [bring]*...proceedings in a US court. Nor am I concerned with the ability of the (equitable) owner to obtain relief for infringement, particularly given that there was no question of infringement at that time. What is relevant is the rights which Pharmasset Barbados had in respect of the invention described and claimed in US 368 as at the date Pharmasset Barbados filed the Pharmasset PCT."*

798. *Mutatis mutandis*, the same observations might be made in the context of this case.

799. In passing, I note that some effort was made by Teva at the hearing of this matter to persuade me that BMS has changed its case on plausibility because it now relies on *Idenix*, this being done (I am told by Teva) in an attempt to distract from *Boehringer* and confuse. Respectfully, I do not see that any of this is so – and it would be a serious matter if lawyers engaged in efforts deliberately to confuse a judge when it came to the applicable law (though again, for the avoidance of doubt, I cannot over-emphasise that I do not see any such efforts to have presented). When Collins J., in *Boehringer*, said what the test was, he started by quoting from Kitchin L.J., as he then was, in *Idenix* and then went on to explain matters further. As I understand BMS's submissions, it has merely taken the test as identified by Collins J. and sought to analyse and explain it. BMS has not sought to distract me from applying *Boehringer* (which would be a futile exercise in any event given that it is a decision by which I am bound and accept myself to be bound). It has but analysed *Boehringer* and made submissions to me as to how it should be applied, and it must be applied.

I. Introduction

800. The basic concept of plausibility can be stated with relative simplicity. But as counsel for BMS noted in his opening submissions, "*There is no bright line definition of the nature or extent of the teaching required to make the claim plausible.*" (*Regeneron* v. *Genentech* [2013] EWCA Civ 93 offers a good example of the difficulties that can present.) Whether the scope of a claim is commensurable to the technical contribution to the art made by a patentee depends on whether it is reasonable to expect that the invention would work. The question usually arises where it may or may not be reasonable to conclude from the teaching of a specification that everything falling within its terms will have the technical properties suggested.

II. *Kirin-Amgen*

801. In *Kirin-Amgen Inc* v. *Hoechst Marion Roussel Ltd* [2005] RPC 9, Lord Hoffman, at §112, spoke of an element of a claim which is stated in general terms being "*sufficiently enabled if one can reasonably expect the invention to work with anything which falls within the general term*", moving on to observe as follows (at §§112-113):

> "112. ....*For example, in* Genentech I/Polypeptide expression *(T 292/85) [1989] O.J. EPO 275 , the patentee claimed in general terms a plasmid suitable for transforming a bacterial host which included an expression control sequence to enable the expression of exogenous DNA as a recoverable polypeptide. The patentee had obviously not tried the invention on every plasmid, every bacterial host or every sequence of exogenous DNA. But the Technical Board of Appeal found that the invention was fully enabled because it could reasonably be expected to work with any of them.*
>
> *113. This is an example of an invention of striking breadth and originality. But the notion of a 'principle of general application' applies to any element of the claim, however humble, which is stated in general terms. A reference to a requirement of 'connecting means' is enabled if the invention can reasonably be expected to work with any means of connection. The patentee does not have to have experimented with all of them.*"

802. (By way of background to *Kirin-Amgen*, the appellant there, Kirin-Amgen Inc was the proprietor of European Patent EP 0148605B2 relating to the production of erythropoietin by recombinant DNA technology. The respondent, Hoechst Marion Roussel Ltd, proposed to import into the United Kingdom erythropoietin, which had been made in the United States by Transkaryotic Therapies Inc by a method referred to as 'gene activation'. Such erythropoietin was referred to as 'GA-erythropoietin'. Kirin-Amgen claimed, in three consolidated actions, that GA-erythropoietin infringed the claims of the patent in suit. TKT and Hoechst claimed a declaration of non-infringement and revocation of the patent.)

803. If, as Lord Hoffman states, "*A reference to a requirement of 'connecting means' is enabled if the invention can reasonably be expected to work with any means of connection*", then the reverse would also seem necessarily to hold true.

III. *Regeneron* v. *Genentech*

804. Coming closer in time, in *Regeneron* v. *Genentech* [2013] EWCA Civ 93, Kitchin L.J., as he then was, put the requirement for plausibility in the following terms, at §100:

> "*It must...be possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible*

or credible. The products and methods within the claim are then tied together by a unifying characteristic or a common principle. If it is possible to make such a prediction then it cannot be said the claim is insufficient simply because the patentee has not demonstrated the invention works in every case."

805. In his opening submissions, counsel for BMS , having referred to the just-quoted observations of Kitchin L.J., posited as a proposition that " *Exactly the same must apply to a claim to a single compound. You do not have to demonstrate that it works, you merely have to give grounds for the skilled addressee reasonably to think that it may.*" At this juncture the following exchange occurred between counsel and myself:

Judge:	...[A]*re you allowed make that distinction...saying well, the patent only relates to one application and the application relates to a whole bundle?*
Counsel:	*I am because the only thing that's claimed – and we are entitled to reduce the claim to the single compound. What I am not allowed to do is to draw any kind of inference from the fact that the claim is only to the single compound to assist you in reaching the conclusion that it is made plausible by the application. I have to get that out of the application….And that is the distinction…. But the point I'm making is I only have to get it out in relation to the claimed compound….My client is entitled to reduce its claim to the single compound. It may well be that on the evidence, you conclude that other compounds which are disclosed in the application would also be plausible on the same basis that -- the evidential basis we are advancing as I've said, that formulation was adopted by Lord Justice Birss in* Akebia*. The point is that if there's a broad claim, it must be justified across its breadth. If it's limited to a single compound then the justification required is equally limited. And in making that distinction, one needs to pay careful attention to the teaching in the specification. In this case the specification of the application.*

806. I respectfully accept this reasoning.

IV. Factor-9/JOHN HOPKINS

807. A narrow claim taken from a broad disclosure is not rendered plausible simply because it is shown after the event that a particular compound the subject of the claim in fact works. That is the underlying reason for the decision in *Case T-1329/04 (Factor-9/JOHN HOPKINS)* (ECLI:EP:BA:2005:T132904.20050628) (which appears also to be the first Board of Appeal decision that makes express reference to plausibility, the Technical Board of Appeal concluding, at 11, "*that there is not enough evidence in the application to make at least plausible that a solution was found to the problem which was purportedly solved"*)."

808. In that case, appeal was brought against a decision of the examining division refusing European patent application No. 94 907 259.9 published under international application No. WO 94/15966 with the title "*Growth Differentiation Factor-9*" (GDF-9) and claiming priority from US 08/003303 of 12 January 1993. The examining division defined the problem to be solved as being the provision of a putative further member of the TGF-ß super family of protein and/or nucleic acid encoding sequences. The appellant filed post-published evidence establishing that GDF-9 was a growth differentiation factor. The examining division, in this context, refused to take into account the teachings of post-published documents showing that GDF9 was a growth differentiation factor because the application did not provide any evidence in this respect. In this regard, the Technical Board of Appeal observed as follows, at 12-13:

"*The said post-published documents are...the first disclosures going beyond speculation. For this reason, the post-published evidence may not be considered....*[T]*o do otherwise would imply that the recognition of a claimed subject-matter as a solution to a particular problem could vary as time went by. Here, for example, had the issue been examined before the publication date of the earliest relevant post-published document, GDF-9 would not have been seen as a plausible solution to the problem of finding a new member of the TGF-β superfamily and inventive step would have had to be denied whereas, when examined thereafter, GDF-9 would have to be acknowledged as one such member. This approach would be in contradiction with the principle that inventive step, as all other criteria for patentability, must be ascertained as from the effective date of the patent. The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve.*"

809. Thus the Technical Board of Appeal held that post-priority date data cannot provide the sole justification for a claimed invention solving the problem it purports to solve. (That is because, in effect, one would be relying on added matter.)

V. *Warner-Lambert* v. *Generics*

810. The question of what is required to render a claim plausible arose directly in *Warner-Lambert Co. LLC* v. *Generics (UK) Ltd (t/a Mylan)* [2018] UKSC 56. There the UK Supreme Court was concerned with the hearing of an appeal and cross-appeal from a decision of the Court of Appeal following the trial of separate actions brought (i) by Generics (UK) Ltd trading as Mylan and by Actavis Group against Warner-Lambert for the revocation of European Patent (UK) No. 0,934,061 on grounds of obviousness and insufficiency and (ii) by Warner-Lambert against Actavis and two others for infringement of the patent. When it came to BMS's submissions, I had the advantage of being led through *Warner-Lambert* by one of the counsel who appeared in that case.

811. Notably, the relevant claims of the patent at issue in *Warner-Lambert* were in Swiss form, *i.e.* claims to the use of a compound in the manufacture or production of a medicament for use in treating a particular therapeutic indication. Actavis had counterclaimed in the infringement action for invalidity and threats. The main focus at the hearing of the Supreme Court appeal concerned the Court of Appeal's findings on the issues of insufficiency and infringement. The patent at the heart of the case concerned a pharmaceutical preparation known as pregabalin which was sold under the trade-mark LYRICA. Pregabalin had been the subject of earlier patent protection but this had expired in 2013. The patent in issue concerned an alleged new use of pregabalin, namely in the preparation of a pharmaceutical composition for treating pain and/or neuropathic pain.

812. As I have already touched upon above, it is notable that *Warner-Lambert* concerned a second medical use patent. The result of this distinguishing factual feature between that case and this is that the applicable principle identified in that case falls to be brought to bear in the context of the very different facts that present here, *i.e.* – as counsel succinctly put matters in BMS's opening submissions – "[A]*pplying the principle to the case where the claim is to a novel compound requires a slightly different approach from that where the claim is to a known compound but for a new use.*"

813. *Warner-Lambert* raised, for the first time in the courts of the United Kingdom, the question of how the concepts of sufficiency and infringement are to be applied to a patent relating to a specified medical use of a known pharmaceutical compound. Patent protection for second use medical patents is difficult to accommodate within the traditional scheme of patent law. Two legal obstacles were

traditionally perceived to present. First, both the product and the process by which it was prepared were known from the original patent and therefore failed the test of novelty. Secondly, its use for a new therapeutic purpose was not itself patentable because the old Art.52(4) of the European Patent Convention prevented the grant of patents for a method of treatment of the human or animal body.

814. Then, in 1984, the Swiss Federal Intellectual Property Office issued a statement of practice that it would be prepared to grant patents for second use medical patents in the following form: 'the use of compound X in the manufacture of a medicament for the treatment of indication Y'. For obvious reasons these are known as 'Swiss-form patents'. Soon after the Swiss Intellectual Property Office made its announcement, the Enlarged Board of Appeal of the European Patent Office adopted a like approach in *Case G-0005/83 (Second medical indication)* (ECLI:EP:BA:1984:G000583.19841205). There is a risk with second use medical patents that they could result in speculative claims, with the result that plausibility acquires an especial significance when it comes to such patents. Lord Sumption comments on this aspect of matters at §§17 and 19-20 of his judgment, where he states among other matters as follows:

> "*17.* *Elementary as it is, it is worth reminding oneself at the outset of the juridical basis on which patents are granted, sometimes called the 'patent bargain'. The inventor obtains a monopoly in return for disclosing the invention and dedicating it to the public for use after the monopoly has expired....*[This] *principle remains the foundation of modern patent law, and is recognised in the case law of both the United Kingdom and the European Patent Office....The principal conditions of validity, novelty, inventive step, industrial application and sufficiency are all, in one way or another, directed to satisfying the principle thus expressed....*
>
> ...
>
> *19.* [The UK Patents Act] *and the corresponding provisions of the EPC assume that an invention will be sufficiently disclosed if the specification enables it to be 'performed'. In the case of a patent for a new product or process, that assumption is almost always correct. The skilled person will discover that it works by replicating it in accordance with the specification. But the assumption is not correct in the case of a second use patent. The invention is not the compound or the process of its manufacture. The skilled person already knows how to make the product from the prior art disclosed in the original patent. The invention consists in the new purpose for which the product is to be manufactured. If... all that needs to be disclosed is the new purpose, which is enough to enable it to be administered to a patient suffering from the relevant condition....*[t]*he result would be that the knowledge which made the identification of the new purpose inventive need not be disclosed at all.*
>
> 20. *The main problem about this result is that it would enable a patent to be obtained on a wholly speculative basis. Without some disclosure of how or why the known product can be expected to work in the new application, it would be possible to patent the manufacture of known compounds for the purpose of treating every conceivably relevant condition without having invented anything at all, in the hope that trial and error might in due course show that the product was efficacious in treating at least some of them.*"

815. It was in this particular context that the UK Supreme Court, in *Warner-Lambert* embarked upon its consideration of plausibility. So while its consideration of this topic is considerably enlightening, one does need to be careful not to apply on a case such as the case before me (which is concerned with claims to a new compound) reasoning of the UK Supreme Court that is directly concerned with a second medical use case.

816. For present purposes it suffices to quote §§35-37 of Lord Sumption's judgment. (Lords Reed and Briggs agreed with Lord Sumption; Lords Hodge and Mance differed slightly. For present purposes, there is no need to distinguish between what they each had to say.) Having considered a number of EPO authorities on the issue of plausibility, Lord Sumption continued as follows:

> "*35. All of these judgments deal with highly fact-specific issues arising from objections or potential objections on the ground of insufficiency. When reading them, it is important not to miss the wood for the trees. The fundamental principle which they illustrate is that the patentee cannot claim a monopoly of a new use for an existing compound unless he not only makes but discloses a contribution to the art. None of them casts doubt on the proposition that the disclosure in the patent must demonstrate in the light of the common general knowledge at the priority date that the claimed therapeutic effect is plausible. On the contrary, they affirm it....*
>
> *36. The Court of Appeal's statement of the effect of the plausibility test has already been quoted....They considered that the threshold was not only low, but that the test could be satisfied by a 'prediction ...based on the slimmest of evidence' or one based on material which was 'manifestly incomplete'. Consistently with that approach, they considered...that the Board's observations in SALK laid down no general principle. I respectfully disagree. The principle is that the specification must disclose some reason for supposing that the implied assertion of efficacy in the claim is true. Plausibility is not a distinct condition of validity with a life of its own, but a standard against which that must be demonstrated. Its adoption is a mitigation of the principle in favour of patentability. It reflects the practical difficulty of demonstrating therapeutic efficacy to any higher standard at the stage when the patent application must in practice be made. The test is relatively undemanding. But it cannot be deprived of all meaning or reduced, as Floyd L.J.'s statement does, to little more than a test of good faith. Indeed, if the threshold were as low as he suggests, it would be unlikely to serve even the limited purpose that he assigns to it of barring speculative or armchair claims.*
>
> *37. Plausibility is not a term of art, and its content is inevitably influenced by the legal context. In the present context, the following points should be made. First, the proposition that a product is efficacious for the treatment of a given condition must be plausible. Second, it is not made plausible by a bare assertion to that effect, and the disclosure of a mere possibility that it will work is no better than a bare assertion. As Lord Hoffmann observed in* Conor Medsystems Inc *v* Angiotech Pharmaceuticals Inc [*[2008] UKHL 49*], *[2008] R.P.C. 28 , [28], 'it is hard to see how the notion that something is worth trying or might have some effect can be described as an invention in respect of which anyone would be entitled to a monopoly'. But, third, the claimed therapeutic effect may well be rendered plausible by a specification showing that something was worth trying for a reason, i.e. not just because there was an abstract possibility that it would work but because reasonable scientific grounds were disclosed for expecting that it might well work. The disclosure of those grounds marks the difference between a speculation and a contribution to the art. This is in substance what the Technical Board of Appeal has held in the context of art.56 , when addressing the sufficiency of disclosure made in support of claims extending beyond the teaching of the patent. In my opinion, there is no reason to apply a lower standard of plausibility when the sufficiency of disclosure arises in the context of EPC arts.83 and 84 and their analogues in s.14 of the Patents Act . In both contexts, the test has the same purpose. Fourth, although the disclosure need*

not definitively prove the assertion that the product works for the designated purpose, there must be something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true. Fifth, that reasonable prospect must be based on what the TBA in SALK...called 'a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se .' Sixth, in SALK , this point was made in the context of experimental data. But the effect on the disease process need not necessarily be demonstrated by experimental data. It can be demonstrated by a priori *reasoning. For example, and it is no more than an example, the specification may point to some property of the product which would lead the skilled person to expect that it might well produce the claimed therapeutic effect; or to some unifying principle that relates the product or the proposed use to something else which would suggest as much to the skilled person. Seventh, sufficiency is a characteristic of the disclosure, and these matters must appear from the patent. The disclosure may be supplemented or explained by the common general knowledge of the skilled person. But it is not enough that the patentee can prove that the product can reasonably be expected to work in the designated use, if the skilled person would not derive this from the teaching of the patent*."

817. A few general points might be made regarding the just-quoted text:

- first, §37 is clearly the key paragraph for present purposes.
- second, of note is the first sentence in that paragraph that "*Plausibility is not a term of art, and its content is inevitably influenced by the legal context.*" Obviously the context of the case that I am deciding is different from the legal context of the case that was before the UK Supreme Court: I am not dealing with a second medical use case.
- third, although all of Lord Sumption's observations are valuable, it seems to me that his fourth point is especially notable, at least when it comes to the facts of this case. In his fourth point, Lord Sumption observes that "[A]*lthough the disclosure need not definitively prove the assertion that the product works for the designated purpose, there must be something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true.*"
- fourth, to the extent that Teva contends that a clear prima facie case for success must be demonstrated in order to establish plausibility, that is clearly wrong when one has regard to Lord Sumption's just-mentioned fourth point.
- fifth, in *Sandoz Ltd* v. *Teva Pharmaceutical Industries Ltd* [2022] EWHC 822, Meade J. was obviously bound by what the UK Supreme Court had decided; hence any reading of Meade J.'s judgment which would have one conclude that he adopted some heightened *prima facie* standard (and I do not see that he did) is bound to lead one into error.

818. Having made these general points, it is useful to make a few points, again by reference to Lord Sumption's judgment, as to what it takes to make a compound plausible:

- first, the law in this area is clearly developing and the difficulty of applying it is made greater because plausibility is inevitably a question of scientific fact.
- second, on a related note, in each case the question is what does the specification in issue, read in the light of the common general knowledge, teach the person skilled in the art? That will depend upon the technology, the nature of the invention and many other factors.

– third, of note too is Lord Sumption's related observation in §37 that "*Plausibility is not a term of art, and its content is inevitably influenced by the legal context*".
– fourth, as Lord Sumption notes across his first to third points:

> "[a] *the proposition that a product is efficacious for the treatment of a given condition must be plausible....*[b] *it is not made plausible by a bare assertion to that effect, and the disclosure of a mere possibility that it will work is no better than a bare assertion...*[c] [plausibility may be established]*...by a specification showing that something was worth trying for a reason, i.e. not just because there was an abstract possibility that it would work but because reasonable scientific grounds were disclosed for expecting that it might well work....[and] [d] [t]he disclosure of those grounds marks the difference between a speculation and a contribution to the art.*"
>
> [Emphasis added].

819. Is it possible to bring these various points together in a coherent whole by reference to the facts and issues in play before me? It is, but rather than re-invent the wheel in this regard, I respectfully adopt the following observations made by counsel for BMS in the course of BMS's opening observations:

> "[A]*ll that the law requires to establish sufficiency* [as is clear from *Warner-Lambert*] *is that there must be something in the specification read in the light of the common general knowledge from which the reader is given reason to believe the claim of factor Xa inhibition may be correct. There is no requirement for proof or prediction. Nor is there a requirement that the result be probable. All that is necessary is that it is reasonable to think that it might be true….The threshold is a low one and is not met only where there is no reason to believe that the claim based on what is in the specification, read in the light of the common general knowledge, will work. In the case of claims to novel compounds, as opposed to second medical use patents, the threshold required to establish that the claim might be correct can and should be no more than* [that] *the compound appears on its face to be one which may have the requisite properties to be an effective factor Xa inhibitor. Data to support the claim are not necessary. Indeed, one sees from the authorities that data are one way, but scientific theory and principle are another.*"

820. As well as the English courts, the Irish courts have addressed the requirement for a patentee to demonstrate plausibility on a number of occasions over the last five years. For present purposes it is sufficient to consider the analysis of the Court of Appeal in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ireland v Boehringer Ingelheim Pharma GmbH & company KG* [2022] IECA 58. There, Collins J, giving the judgment of the court, conducted a review of relevant United Kingdom and European Patent Office authorities, including the above-considered decision of the United Kingdom Supreme Court in *Warner-Lambert Co. LLC* v. *Generics (UK) Ltd (t/a Mylan)* [2018] UKSC 56.

821. The relevant section in the decision of the Court of Appeal in *Boehringer* runs from §§149–179. The analysis of Collins J. analysis makes clear that there is no requirement for experimental data to support a claim. At §169, he quotes the statement by the Technical Board of Appeal in Case T-1642/07 *Arch Development Corporation* that "[T]*he fact that the disclosure in a patent application is merely theoretical and not supported by experimental data is in itself no bar to patentability or to the presence of a technical effect being acknowledged*", whilst pointing out that a bare assertion of technical effect is insufficient. (In that case, it will be recalled, the Technical

Board of Appeal referred questions on the principle of free evaluation of evidence and the notion of 'plausibility' in the context of inventive step to the Enlarged Board of Appeal. The core dispute in *Sumitomo* concerned European patent EP 2 484 209 regarding an insecticide composition. According to the patent, two compounds known for their insecticidal effect had a synergistic effect when mixed. In dealing with the issue of plausibility the Enlarged Board of Appeal considered that that concept did not amount to a distinctive legal concept or a specific patent law requirement, but rather was a "*generic catchword*". (This avoided the difficult issue of whether technical effect is a matter of *ab initio* plausibility or implausibility.) According to the Enlarged Board, the relevant standard for the reliance on the purported technical effect when assessing whether or not claimed subject matter involves an inventive step is what the skilled person, with common general knowledge in mind, would understand at the filing date from the application as originally filed.)

822. The above-mentioned observation in *Arch* (that the disclosure in a patent application is merely theoretical and not supported by experimental data is in itself no bar to patentability or to the presence of a technical effect being acknowledged) is also referred to by the Enlarged Board of Appeal in Case G0002/21 *Sumitomo* (ECLI:EP:BA:2023:G000221.20230323) at §69). By way of background to *Arch*, that was summarised as follows by Collins J., at §169:

> "*The application there was for a patent for* 'methods and compositions for viral enhancement of cell killing' *involving the use of the herpes simplex virus in combination with a suitable chemotherapeutic agent, for use as an alternative anticancer therapy. The application was refused by the examining division, inter alia, because of the absence of experimental data showing the synergistic effect of proposed combination therapy. The Board of Appeal observed that there was no requirement in the EPC that a patent application should include experimental evidence in support of patentability or a claimed technical effect. Hence, it continued,* 'the fact that the disclosure in a patent application is merely theoretical and not supported by experimental data is in itself no bar to patentability or to the presence of a technical effect being acknowledged' *(para 18). In* Arch, *the* 'theoretical statements' *in the patent application were clearly considered sufficient by the Board, particularly because, in its view, the technical problem to be solved was properly formulated in less demanding terms than it had been by the examining board. The patent application as filed addressed* 'expressis verbis the claimed subject matter and potentiation (additive until synergistic killing effect on cells/cancer cells)' *(para 18) and the technical effect was announced* 'albeit at a theoretical level' *in the application as filed (para 20). The Board's statement at para 22 that it saw* 'no grounds for doubting' *that the combination therapy would achieve an increase in the level of cell killing must be understood in the light of those earlier observations and cannot, in my view, be read as formulating any general principle that assertions as to technical contribution, however bare, must be taken at face value in the absence of substantiated doubts. I am fortified in that conclusion by the fact that, in the course of its decision in* Arch*, the Board refers to* John Hopkins *without any suggestion that it considered it to be incorrect (at para 21).*"

823. Notably, at §172 of his judgment, Collins J. observes that "[T]*he issue of whether a claimed technical contribution is plausible is context dependent. Much will depend on the nature of the invention, the nature and breadth of the claimed technical contribution, the disclosure in the specification and what is the relevant common general knowledge.*" This last-quoted comment reinforces the point that everything depends upon the facts of each individual case. Consequently, the particular turn of phrase used to embody the test for plausibility will, as Collins J. noted, be affected by the relevant facts; differences between the formulations used by different tribunals are not significant. Many of the cases in which the issue of plausibility has arisen concern factual circumstances far removed from those of the present case. Whilst those principles are obviously important, they do not constrain my approach to or assessment of the facts before me in the within proceedings.

824. At §§174–179, Collins J. summarised his conclusions on the applicable test. At §174, Collins J. adopts, in the following terms, the test as stated by Kitchin LJ in *Idenix* (at §114), *i.e.* that "'[I]*n light of the teaching in the specification and the common general knowledge*' there *must be a real reason for supposing that the claimed invention will indeed have the promised technical effect.*'" Collins J. later moves on to observe as follows at §176:

> "*Whether a* 'real reason' *is disclosed requires assessment on a case-by-case basis and cannot be the subject of any* a priori *rule. Proof of efficacy – even to a* prima facie *standard – is not required. I agree...that Lord Sumption's judgment in* Generics (UK) *v.* Warner-Lambert Co *is not to be read as requiring* prima facie *proof. On the other hand, mere assertion will not suffice. There must be something that demonstrates that the claimed technical contribution is not speculative and that will cause the skilled person to think that there is a real basis for thinking that the claim is true and that* 'the claimed invention will indeed have the promised technical effect'. *I do not think that this formulation differs in any material way either from the test formulated by Lord Sumption in* Generics (UK) *v.* Warner-Lambert Co *at para 37* ('there must be something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true') *or the test suggested by Lord Hodge at para 179 (*'the specification must disclose some scientific reason for thinking that the [invention] might well have the claimed … effect'*). Insofar as there is a conceptual difference between those two formulations of the applicable test, it has no practical significance here in any event, as I shall explain.*"

825. However one formulates the test in terms of the wording deployed in that formulation, all the test requires is a reasonable technical basis for concluding that the patented molecule might well have the claimed effect (per Lord Sumption as quoted by Collins J. at §176 of *Boehringer*). This is the basis on which I have approached the facts on the basis of the evidence adduced by the parties in these proceedings. (As I have stated previously above, in *Warner-Lambert* Lords Reed and Briggs agreed with Lord Sumption, with Lords Hodge and Mance differing slightly. For present purposes, there is no need to distinguish between what each peer decided.)

vii. Data

826. I should perhaps pause for a moment to touch on the issue of data. As counsel for BMS stated in the just-quoted extract from BMS's opening submissions, as respectfully adopted by me, data to support a claim is not necessary. It is clear from the evidence before me (including, notably, the evidence of Dr Edwards, the medicinal chemist called by Teva) that data to predict or determine that a compound is an effective factor Xa inhibitor therapeutically would include a wide variety of information, including potency data, selectivity data, and oral bioavailability data. So it is not the case that with potency and sufficiency data the specification in this case would be sufficient and that without such data it is not. Of course, as counsel for BMS stated in the just-quoted extract from BMS's opening submissions, as respectfully adopted by me, "[T]*he threshold required to establish that the claim might be correct can and should be* [that]*...the compound appears on its face to be one which may have the requisite properties to be an effective factor Xa inhibitor*", *i.e.* the specification must give the skilled reader reason to believe that the molecule is a potential candidate. However, that can be done in various ways, ways that do not require potency data, selectivity data, oral bioavailability data, or other particular data. As counsel for BMS stated in BMS's opening submissions, again in terms that I respectfully adopt:

> "*It is sufficient to provide information which demonstrates that the molecule has a suitable structure to engage with factor Xa as ligands which have been shown to bind, or which it is clear from the specification the authors have found to bind and has an overall make up with, in the light of the common general knowledge, may reasonably be expected to give it the appropriate binding selectivity and biological properties to*

make an effective inhibitor."

VI. *Sumitomo*

827. As I mentioned in the opening chapter, up to the decision of the Enlarged Board of Appeal at the European Patent Office in Case G2/21 *Sumitomo*, the Irish and English courts have held that if a claimed invention is not plausible, there can have been no technical contribution with the consequence that the claimed invention lacks inventive step and/or the patent is insufficient.

828. In *Sumitomo* the Technical Board of Appeal referred questions on the principle of free evaluation of evidence and the notion of 'plausibility' in the context of inventive step to the Enlarged Board of Appeal. The underlying case in *Sumitomo* concerned European patent EP 2 484 209, which pertains to an insecticide composition for controlling an insect pest. According to the patent, two compounds already known for their respective insecticidal activity had a synergistic effect when used as a mixture.

829. Under European Patent Office case-law, it is for a patent applicant or proprietor to demonstrate that the purported technical effects of a claimed invention have been achieved. In dealing with the issue of plausibility the Enlarged Board of Appeal considered that that concept did not amount to a distinctive legal concept or a specific patent law requirement, but rather was a "*generic catchword*". (In reaching this conclusion the Enlarged Board of Appeal essentially avoided the difficult issue of whether technical effect requires one to demonstrate *ab initio* plausibility or *ab initio* implausibility.)

830. According to the Enlarged Board, the relevant standard for the reliance on the purported technical effect when assessing whether or not claimed subject matter involves an inventive step is what the skilled person, with common general knowledge in mind, would understand at the filing date from the application as originally filed.

VII. An Unexpected Proposition as to Plausibility

831. In his closing oral submissions, counsel for Teva made an unexpected proposition as to plausibility. Thus he suggested that Norway does not have the same law of plausibility as Ireland and the UK as one of the reasons why I should not give the same weight to a decision in Norway as to the decision in the UK. It may have been a slip of the tongue: the legal team for Teva was so distinguished that I suspect it was. However, I must respectfully note that it is a mistaken proposition. Plausibility is a concept which has been created under the European Patent Convention. It was developed by the tribunals of the European Patent Office. Lord Sumption's statement of the law in *Warner-Lambert* and his summary of principles at §37 of that case is derived from, and intended to be a distillation of, a detailed analysis of the relevant European Patent Office jurisprudence. That jurisprudence, I cannot but respectfully note, applies equally in all other states that are contracting parties to the European Patent Convention. Of course it may be that the domestic courts in any one state signatory to the European Patent Convention will have had cause to consider the notion of plausibility more times and/or in greater detail than the courts of another such signatory state and thus will be more familiar with what the concept involves and what issues may present.

VIII. The Person Skilled in the Art

832. When designing a proposed new pharmaceutical molecule, the design work is done by medicinal chemists. They work with pharmacologists who test and evaluate the properties of the molecules that have been designed. Using the knowledge gained from the assessment of the properties, the chemists will adjust the structure of a molecule in an endeavour to improve and optimise its properties. Alternatively, if a particular molecule does not appear to have any promising characteristics, a different molecule will be created, using the knowledge learned from the previous failure. The process is iterative and it is common ground that in many cases no useful product

results, although the learning from the work which has been done can be taken forward and used to inform the next attempt. Once a molecule with sufficiently interesting properties to enable it to be tested *ex* or *in vivo* has been identified, the pharmacokineticist will be called in to test and evaluate its biological properties.

833. My task in these proceedings is to interpret the patent and the application from the perspective of a skilled person or skilled team, as explained by Costello J., for the Court of Appeal, in *Gilead Sciences Inc v. Mylan SAS* [2021] IECA 22 at 37:

> "[T]*he patent is to be construed through the eyes of the skilled addressee. He is – or as the case may be, they are – a hypothetical construct. The skilled addressee is thus a person or persons with practical knowledge or experience of the kind of work in which the invention was intended to be used. They are deemed to have the knowledge which any worker in the area would be expected to have as part of their general knowledge which they would have had as of the priority date.*"

834. I note in passing, as indeed Teva has noted in its closing submissions, that the skilled person is also uninventive. As Lord Reid observed in his speech to the House of Lords in *Mills & Rockley (Electronics) Ltd* v. *Technograph Printed Circuits Ltd* [1971] FSR 188 at 193 (consistent I note with the law in this jurisdiction):

> "[T]*he hypothetical addressee is a skilled technician who is well acquainted with workshop technique and who has carefully read the relevant literature. He is supposed to have an unlimited capacity to assimilate the contents of, it may be, scores of specifications but to be incapable of scintilla of invention. When dealing with obviousness, unlike novelty, it is permissible to make a 'mosaic' out of the relevant documents, but it must be a mosaic which can be put together by an unimaginative man with no inventive capacity*."

835. (By way of background, in *Technograph*, the plaintiffs brought an action for infringement of their patent relating to printed circuits. They alleged that the defendants' method of making printed circuits was an infringement of their patent; however, the defendants denied that their method constituted 'printing' within the meaning of the patent. The defendants challenged the validity of the patent on, amongst other matters, the ground of obviousness.)

836. In these proceedings, Teva submits that the skilled team comprises a skilled medicinal chemist and a skilled pharmacologist. That is common ground with BMS. The dispute is whether a skilled pharmacokineticist is also part of the skilled team. My view on this last matter can be shortly stated: the pharmacokinetic description on page 6 of the application is agreed by every expert other than Professor Taft to be in the nature of a 'wish list' which is wholly within the CGK, and it is admitted (even by Professor Taft) that there is no pharmacokinetics data in the application. Consequently there is nothing of practical interest to a pharmacokineticist in the application. The bulk of the specification in this case is directed to a medicinal chemist, *i.e.* someone who designs potentially therapeutic molecules. The vast majority of the document is devoted to chemical structures and the synthesis of the molecules the subject of the disclosure. There are short passages concerned with the desirable biological properties of the molecules and the utility of the invention. These passages are directed more to the pharmacologist. I am therefore of the view, based on the whole of the evidence before me, that the skilled team comprises a skilled medicinal chemist and a skilled pharmacologist only.

IX. THE PHARMACOLOGY EVIDENCE

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The Evidence of Dr Gallagher

A. Introduction

837. Dr Gallagher is a distinguished physiologist and pharmacologist who has worked in the academic and private (pharmaceutical) sectors and previously published a book on anti-thrombotics. In his first witness statement, Dr Gallagher states, amongst other matters, as follows (at §§3.1-3.2):

> "*I was asked by Pinsent Masons (Ireland) to act as an expert witness in the proceedings listed above. I understand that Teva has brought an action against BMS Holdings Ireland Unlimited Company…to revoke BMS' European Patent IE No 1 427 415….First, I was asked to consider what a pharmacologist would have known about the pharmacological aspects of coagulation and related therapies, in particular thrombin and FXa inhibitors, as of 21 September 2001…which I was told was the key date for the proceedings and which I also now know is the priority date of the Patent*"

and (at §1.2) of his second witness statement:

> "*I have been provided with Professor Morrissey's report, along with the documents he provided and those with which he had been provided. I have also been provided with the expert reports of Dr. Young and Dr. Taft.*"

838. Subject to para.4 of this judgment, an abridged version of Dr Gallagher's written evidence is set out at Appendix 4. I respectfully invite readers of this judgment to read that appendix and then resume reading here.

B. Examination

1. Factor Xa as a focus of research

839. Asked by counsel for Teva why Factor Xa became the focus of research in the area of antithrombotics in the period between 1995 and 2000, Dr Gallagher indicated as follows:

> "[S]*ome companies were working on thrombin, some were working on Xa. I worked for a company that thought Xa was the best. And of course, a lot of other companies did as well. The first reason that we thought Xa would be better is....*[i]*f you're going to decide to inhibit thrombin, you have to inhibit a lot of thrombin. That means a lot of inhibitor molecules. But if you could stop, or at least minimise...the production of thrombin and thereby the production of fibrin by hitting the molecule in charge of making thrombin, that might be a more efficient way to go. So...the theory was that a relatively small amount of a thrombin, of a Xa inhibitor might show big dividends in terms of how much thrombin generation it inhibited.*"

840. Counsel for Teva referred Dr Gallagher to para. 50 of the agreed CGK document and asked whether Dr Gallagher agreed with same. Dr Gallagher thought it a good summary. Paragraph 50 of the agreed CGK document states as follows:

> "*Factor Xa was identified as a promising target for the development of new synthetic anticoagulants following the isolation and characterisation in the late 1980s of the first naturally occurring specific factor Xa inhibitor, antistasin, isolated from leeches,*

and Tick Anticoagulant Peptide (TAP). TAP is a potent and specific inhibitor of factor Xa which inhibits thrombosis without causing excessive bleeding."

2. What a Skilled Pharmacologist Would Have Been Looking For

841. Counsel for Teva then asked what – after having identified Factor Xa as the appropriate enzymatic target in 1995 to 2000, particularly 2000/2001 – a skilled pharmacologist would have been looking for in an effective Factor Xa inhibitor at that time. To this, Dr Gallagher responded as follows:

"*What we were looking for was direct inhibitors that would be able to inhibit Factor Xa free in plasma, but also particularly in this prothrombinase complex, because that is where most of the thrombin is made. So, we were looking for small molecule direct inhibitors that were highly potent for binding to Factor Xa. So, potency was important. However, because this is in a family of proteins called serine proteases, of which there are very many...in the coagulation cascade, some...for digestion, some...for other things – it had to be very specific, you know, it had to be unique for Xa and not be hitting some of these other proteins that had similar structures.*"

3. The Zhu and Scarborough article

(Zhu, B. and R. Scarborough, "Recent advances in inhibitors of factor Xa in the prothrombinase complex" (1999) 1(1) *Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs* 63-88.)

842. Counsel had this article handed to Dr Gallagher to determine if he agreed with its summary of what the target was in terms of Factor Xa inhibitor research around the time of its publication. Counsel referred in particular to the following text therein (at 63-64):

"*Several review articles on factor Xa (FXa) inhibitors have already been published. This is a review of patent literature and articles from January 1998 to January 1999 relating to the development of FXa inhibitors as novel anticoagulants. During the past year, there has been an explosive increase in the amount of information relating to the interactions of FXa inhibitors with FXa, and to the design and development of highly potent and specific inhibitors of FXa assembled in the prothrombinase complex.*

...

These inhibitors should: (a) be highly potent against FXa and FXa in the prothrombinase complex; (b) be highly specific for FXa versus thrombin, trypsin and other fibrinolytic enzymes such as tissue plasminogen activator (t-PA), APC and plasmin; (c) exhibit the desired in vivo efficacy, high oral bioavailability and long duration of action; and, (d) not cause serious bleeding complications at efficacious doses. In other words, ideal antithrombotic agents should compensate for the clinical limitations of warfarin, heparin and LMWH."

843. Dr Gallagher agreed that this text summarised what was being looked for.

4. Potency

844. Counsel queried what level of potency would have been looked for in 2001 in terms of an effective Xa inhibitor as a potential therapeutic. Dr Gallagher indicated that "*Most of us were looking for the same level of potency. And that level of potency was a Ki that was in the nanomolar or sub-nanomolar range.*"

845. Later, counsel asked what kind of test Dr Gallagher would one use to test for potency if one was developing a Factor Xa inhibitor. To this, Dr Gallagher responded as follows:

> "*There were pretty standard tests available. Chromogenic assays they were called. Usually they'd be in a format with a 96-well plate and you'd put different concentrations and use a spectrophotometer to detect colour changes which you could quantify. And with that, usually the first test that we would do – and most places, I think, were the same way – was the Ki, the disassociation constant of the inhibitor with the enzyme. And using these fairly standard kits, you could establish, well, is the Ki 1 nanomolar or 0.1 nanomolar or, you know, 10 micromolar or something like that? So, there is a standard way of doing it.*"

846. Asked what level of potency one would look for in an initial screening of a library of compounds, Dr Gallagher responded as follows:

> "[T]*his was an era when mass screenings were just starting to be done. And, for example, at Parke-Davis, where I worked, there was a compound library of a million compounds. And the idea would be to pick a threshold to get from a million down to a hundred or fifty. And most companies did that as well. When we were working with Burlex, for example, who eventually developed CI-1031, which had a lot of promise, you know, they basically did the same thing. So, the thresholds might be set at, for certain things we would set it at 30 micromolar and other people would do 10 micromolar, such as in the patent application. And that's a way of, you know, okay, instead of dealing with thousands of molecules, you've got a handful that are going to have certain structural things in common and so you've got a starting point.*"

847. Counsel asked whether para.111 of the agreed CGK document identified the kind of threshold that one would be looking for as a starting point. Dr Gallagher agreed that it would. Paragraph 111 of the agreed CGK document states as follows, under the heading "*Starting point*":

> "*The skilled medicinal chemist would often first become involved in a new drug discovery project once the biological target had been identified. Their first task would be to work with the skilled pharmacologist to identify a compound (or class of compounds) as a starting point for the project (in this case potential inhibitors). The objective would be to find a compound or compounds with sufficient activity against the target, and possibly selectivity for that target over other enzymes, which could form a starting point for synthesising analogues, which may have improved properties. Starting points can typically be identified in three different ways: i) finding known compounds published in the literature; ii) starting from the endogenous substrate; and iii) high-throughput screening, which was already in use in 2001, and in which tens or hundreds of thousands of compounds can be screened using automated assays.*"

848. Asked again what would have been regarded as the necessary level of potency in 2001, Dr Gallagher responded "*in the nanomolar range, ideally in the sub-nanomolar range.*"

5. Selectivity

849. Turning to selectivity, counsel for Teva asked what Dr Gallagher was trying to make the inhibitor selective against. The following exchange then occurred:

> Dr Gallagher: ...[M]*any of the coagulation proteins are classified as part of the serine protease group....*[S]*erine proteases are also part digestive system, and there's some in immune. So there's a lot of serine proteases floating around in us. The fact that they're serine proteases means that they may have some structural*

commonalities. So...you want a unique Factor Xa inhibitor that's going to inhibit Factor Xa at a very high level of potency, but you don't want it...inhibiting any of these other serine proteases, because that will lead to side effects of one sort or another....

Counsel: *Would you agree that there's little risk of there being an overlap between the inhibitors that would inhibit Factor Xa and inhibitors that would attack other proteases?*

Dr Gallagher: *It's interesting how you put the question, 'little risk'. You know, my job working as a pharmacologist in this setting is to deal with data and I would never assume that simply because...it's pretty potent against Xa, that I can just step away and say 'Well, it's probably not going to affect those others'....[T]ests would have to be done.*

6. Chromogenic Assay

850. Counsel noted that Dr Gallagher had mentioned the use of chromogenic assays when it came to identifying the potency of compounds. Elaborating on this, Dr Gallagher indicated as follows:

"*The chromogenic assay is designed to be rapid and give you directional notions of ID. The constant, the Ki, that calculation is hard and fast. But the conditions of the test are not very physiologic. The idea is to make it easy to get numbers quickly. And so it's a relatively simple solution that, you know, the enzyme's in there and you add different concentrations of a potential inhibitor. And in fact the substrate that you're using, that you're measuring the colour change from, is in fact an artificial substrate, you know, it doesn't simulate what's going on in the blood or the plasma. So, it's a good way to determine a constant, but it does not represent true physiologic conditions.*"

7. Oral Bioavailability

851. Counsel asked Dr Gallagher to explain the concept of oral bioavailability and what role it played in the development of Factor Xa inhibitors in 2001. In response, Dr Gallagher indicated as follows:

"[T]*he context for that is that...most of us were looking for...a replacement for Warfarin, which was the only orally bioavailable anticoagulant. And it's very indirect, it operates by reducing the enzyme's production of certain other coagulation factors. It'd been around for a long time but, you know, it had some pitfalls. So, the idea was we wanted small molecules that could get into the prothrombinase complex and into the messy conditions of a clot. But a small molecule is also more likely to be orally bioavailable; you can take it, in contrast to like proteins or heparins or things like that. And so the real goal was not only potent and highly selective, but orally bioavailable and ultimately with enough of a half-life that you only had to take it once or twice a day.*

...

[The concept of half-life is] *basically a measure of how long the inhibitor is in the blood. So, you take it, it has to be absorbed and, you know, some of it's absorbed, some of it's not absorbed. But it's in the blood. And then plotting it versus time, you plot the concentration and it drops off. And the half-life is...a convenient mathematical way of saying 'Okay, it's peaked; okay, now it's halfway from its peak'. And that gives you a rough idea of how long you're going to have enough of that material in the bloodstream to be exerting an effect.*"

8. Interactions with medicinal chemist

852. Counsel for Teva asked Dr Gallagher, in his role as a pharmacologist and on a drug development team, (i) what his interaction would be with a medicinal chemist, and (ii) what role he would play in terms of engaging with the medicinal chemist in the drug development pipeline? In response, Dr Gallagher indicated as follows:

> "[T]*hese kinds of projects start with the chemists....*[T]*hey've got to come up with the structures and synthesise things that we can help them test. And...there's a lot of overlap from one department to the next, there's handoffs as you meet different development milestones. So, the pharmacologists and particularly the biochemists who were working for me at the time would work closely with the chemist to do quick tests - you know, 'Did this one hit our potency idea? It didn't. Well, maybe we've got to change part of the molecule'. So that would be our interaction with them. And then at the other end we would be interacting with...like the pharmacokinetics people, to deal with oral bioavailability. So, the interaction would be very iterative and go back and forth.*"

853. Later in her examination, counsel referred to para.109 of the agreed CGK document, where there is a description of the "*trial and error process*" and asked for Dr Gallagher's confirmation that "*that is your agreed evidence*". Dr Gallagher indicated that §109 was a good indication of what he meant. §109 of the CGK states as follows:

> "*Research into new drugs is a trial and error process, which means that drug discovery is difficult, expensive and time-consuming. In 2001, it would typically take a minimum of 2–3 years to go from the start of a project to a clinical candidate, although the vast majority of projects would not deliver a clinical candidate. Even then, of these candidates the vast majority would fail in clinical trials, which themselves can take up to a further 10 years. It would not be unusual for a medicinal chemist to spend their entire 30–40 year career synthesising compounds without ever having worked on a marketed drug.*"

9. Pharmacologists, enzymologists, and biochemists

854. Counsel asked whether Dr Gallagher would expect a pharmacologist to be familiar with the enzyme that he was targeting, to be a person who has a background and experience in the particular activity being researched. In his response, Dr Gallagher indicated:

> "[E]*nzymologists, who know about the kinetics of enzymes and stuff like that, that's usually the biochemists who really know that kind of stuff and the kinetics of enzyme*[s]....[A] *pharmacologist, in my experience, we dealt with...the kinds of tests that told us what was going on – you know, the Ki tests, the selectivity and so forth. The biochemists tended to get more into the detail of the molecules....*[I]*f there was a real issue related to structure, Vmax, various kinetic parameters associated with this enzyme or that enzyme and interactions, the biochemist would be the expert on that. But the biochemist wouldn't necessarily be able to do the things I could do either*".

10. Predicting and Testing

855. Referring to how Dr Gallagher had described the process of engagement with the medicinal chemist to be an iterative one, counsel for Teva asked Dr Gallagher what his view was of the proposition "*that you could basically predict, based on structure, what the likely inhibitory effect of an antienzyme inhibitor was going to be*". The following exchange then occurred:

> Dr Gallagher: [M]*y interactions with medicinal chemists over the years has been*

up and down, so take that as a caveat. There's a lot known about the structure of Factor X - and in fact the crystal structure, I think, was solved in 1993/94, something like that. So, the active site has got these pockets and little holes and stuff. And the chemists, one of the things that they would do - and sometimes they would use computer modelling to help them with this - is say 'Well, if we put this here and that there, it'll fit just right'. And sometimes they were right and sometimes they were wrong. In the end, there was no replacement for synthesising at least a small amount of the molecule and testing it.

Counsel *So, would you have been satisfied, based on structure, that you could understand what the likely activity of an anti-inhibitor was going to be?*

Dr Gallagher: *No...*

856. The following day, counsel returned to Dr Gallagher's evidence that "*you can't predict activities in structures*". Dr Gallagher expanded on what he meant in this regard, stating as follows:

> "[W]*e know things about chemistry and the structure of...enzymes...*[Y]*ou can plan and synthesise various structures, because you think 'Well, this might fit here and that might fit there'. But in the end, you still have to test; you have to make sure that in fact it fits what the way you think it does.*"

857. Asked by counsel to describe such tests, Dr Gallagher did so and also indicated that §65 of the agreed CGK was a correct summary of some of those tests. Paragraph 65 of the agreed CGK states as follows:

> "*PT and aPTT are standard assays that measure the time it takes blood or plasma to clot after adding a clotting stimulator (thromboplastin for PT and partial thromboplastin for aPTT). This can be carried out on blood obtained from animals or on human blood. These assays are routinely used in clinical practice to monitor patients treated with warfarin or heparin. In a drug development program, a compound would be given either orally or intravenously to an animal. Blood samples are taken prior to compound administration and a specific time after compound administration. The plasma component is separated from the blood samples and each plasma sample is subjected to PT and aPTT assays. In 2001, such assays were automated using special instruments that measured clotting spectrophotometrically by detecting changes in light transmission through the sample as a clot formed. A comparison is then made between the time taken for the plasma to clot in plasma samples obtained after compound administration compared to the control sample obtained prior to compound treatment.*"

858. Asked by counsel whether the tests mentioned in the last-quoted text were the tests "*that you would expect to see if you were engaged in the type of iterative trial and error process that you would be in drug development engagement as a medicinal chemist*", Dr Gallagher indicated as follows:

> "[T]*he iterative back and forth with the medicinal chemist, the main [things] they'd be looking at initially would be, like, potency and selectivity. And then when we have narrowed things down and it looked like we had some, not necessarily the candidate, but a group of candidates, that's when we would start doing these what we would call ex vivo tests, which is a bigger challenge for the drugs, the inhibitors, because it was in plasma and plasma proteins and other things. So, it's a more complicated physiological mix than the relatively simple kinds of situation or conditions that characterise the Ki determinations....*[I]*n vivo is putting it into an animal. Ex vivo is*

removing blood samples and looking at plasma or whole blood on the bench."

859. Asked whether one would need to do an *ex vivo* test in order to get a proper indication of the effectiveness of an inhibitor, Dr Gallagher indicated that this would be standard.

860. Counsel then asked Dr Gallagher to describe what the *in vivo* testing in the form of an animal shunt model would involve. Dr Gallagher described this type of testing in the following terms:

> "*That is one type of in vivo test, an experimental animal model. Obviously, we can't put it right into humans, but we do want to challenge the inhibitor candidates in a setting that is going to be like humans. So, almost* [all?] *of these studies were done in animals – rats, rabbits, dogs, sometimes monkeys. Academics tended to use mice because they were smaller animals....The rabbit model that's described is one example of it....*[B]*asically, the idea is you'd connect an artery to a vein in a rabbit or rat – you can also do* [it] *in rats – and then you put a thread inside a plastic tube that's connecting those two blood vessels and that creates a zone where thrombus will form. And the end point for the evaluation is the weight of the thrombus after a certain period of time. So, you give different amounts of drug over different periods of time and compare the weights of the thrombus because of the clot. There were variants of it, we worked on a variant of it at Parke-Davis. But it is a quite standard model and it was the kind of step through to Ki potency, selectivity, ex vivo, PTs/aPTTs. And then in vivo, okay, how does it work when we're really challenging it?*"

861. Counsel for Teva led Dr Gallagher to §168 of the CGK, where it is stated that "*The amount of material needed to perform an* in vivo *preclinical pharmacokinetic experiment depends on the goal of the experiment and the species of animal tested*" and asked if Dr Gallagher agreed with this statement. Dr Gallagher agreed with this statement, adding "*It also depends on the properties of the compound*".

862. Counsel for Teva then led Dr Gallagher to §4.3 of his second witness statement. There, Dr Gallagher replies to the witness statement of Professor Morrissey (considered later below) and the notion that 3.07g would be enough to run an AV shunt model, with Dr Gallagher observing as follows in this regard:

> *"I agree that this quantity might have been sufficient for some testing. The amount of testing that would have been possible would depend on the biological properties of the compound including potency and selectivity. Therefore it is not possible to know what the extent of the testing might have been and the skilled person would need further information that is not in W0652 to determine the same.*"

863. Having read out this observation, counsel asked Dr Gallagher to confirm (and he did) that it was his evidence "*that if you were to try and undertake some of these tests, as the agreed CGK document says, it will depend on the goal of the species and, as you say at 4.3,* [the] *biological properties of the compound*".

11. Skilled Person

864. Dr Gallagher acknowledged that he understood the concept of a skilled person. Asked, after reviewing 652, who he thought would have a practical interest in the patent application, Dr Gallagher responded as follows:

> "*It's primarily a chemistry document, so my first reaction was this is something a chemist should review. And based on some of the assertions that are made at the beginning of the patent, it occurred to me that, well, a pharmacologist should also take a look at this. But there isn't much to review for a pharmacologist*".

865. I interjected at this point that in his report Dr Gallagher had referred to both a medicinal chemist and a pharmacologist as part of the skilled team and queried whether he still thought it would be both. To this, Dr Gallagher responded that "*Well, you needed a pharmacologist to take a look at the attributes that they were collecting*".

866. When counsel for Teva mentioned that BMS contended that there should also be (i) a pharmacokineticist, Dr Gallagher disagreed, saying "*There's nothing for a pharmacokineticist to look at in this. So, I don't think it would be necessary*", (ii) a clinician, Dr Gallagher again disagreed, saying "*There is nothing for a clinician to look at either.*"

867. Later in her examination, counsel for Teva put to Dr Gallagher an assessment by Dr Morrissey (a witness for BMS whose evidence is considered later below) as to who would be a member of the skilled team, Dr Morrissey opining in his first witness statement as follows:

> "*The majority of the disclosure in the patent relates to the development and synthesis of new chemical structures which would primarily be of interest to the medicinal chemist. However, as the biological target is factor Xa and the Patent includes descriptions of the methods of evaluating the efficacy of factor Xa inhibitors, I believe that a biochemist with experience in the field of thrombosis and hematology and a detailed knowledge of the coagulation cascade would also be part of the skilled team.*"

868. Asked if he shared the same view, Dr Gallagher indicated as follows:

> "*A good deal of this is biochemistry, I agree with that. And I would qualify, saying that I sort of agree with his comment to the extent that we're talking about a biochemist who knows how the coagulation cascade works and has some understanding of how you intervene. And that's where biochemistry and pharmacology start kind of blending into each other. So, is it possible to answer this question by saying I partially agree?*"

869. Counsel for Teva also brought Dr Gallagher to §109 of the agreed CGK where the following is stated under the heading "*Drug Discovery Process*":

> "*Research into new drugs is a trial and error process, which means that drug discovery is difficult, expensive and time-consuming. In 2001, it would typically take a minimum of 2–3 years to go from the start of a project to a clinical candidate, although the vast majority of projects would not deliver a clinical candidate. Even then, of these candidates the vast majority would fail in clinical trials, which themselves can take up to a further 10 years. It would not be unusual for a medicinal chemist to spend their entire 30–40 year career synthesising compounds without ever having worked on a marketed drug.*"

870. Recalling that Dr Gallagher had mentioned about research being an iterative process, counsel stated that her understanding of Dr Gallagher's evidence was that this process "*would include going back between the medicinal chemist and pharmacologist on the skilled team, is that correct?*". To this question, Dr Gallagher responded that "*In the pharmaceutical environment that I worked in, that's the way it would work.*"

871. Asked whether, as a skilled pharmacologist on the skilled team, there was any reason Dr Gallagher could see, from the set of skills that he brought to bear in reading the patent application, to believe that there was an effective Factor Xa inhibitor here. Dr Gallagher answered this in the negative, adding "*Remember, I'm looking for numbers, for data that tell me that this compound has this Ki and this compound has that Ki, that sort of thing. And there's no information in here.*"

12. Aim of Inventors

872. Asked what he considered the inventors were trying to achieve, Dr Gallagher indicated as follows.

> "[W]*hen I read the beginning of the application, I thought they were trying to identify Factor Xa inhibitors....*[S]*ome confusion resulted later,...because they talked about testing for thrombin and looking for inhibitors of other serine protease inhibitors. So, the whole picture was a little confused....I wish I could say that I had confidence...that they were just looking for Factor Xa inhibitors, but they mentioned the possibility of identifying other types of inhibitors too*".

873. Counsel for Teva drew the attention of Dr Gallagher to the fact that at p.1 of the patent application, under the heading "*Field of the Invention*", the following text appears:

> "*This invention relates generally to lactam-containing compounds and derivatives thereof which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment of thromboembolic disorders*",

and asked for what purpose did he believe the inventors were developing, or seeking to develop, Factor Xa inhibitors, based on that description of their own invention – to which Dr Gallagher responded "*Just as it says, as anticoagulant agents for treating thromboembolic disorders.*"

874. Turning to p.6 of the patent application, counsel for Teva queried whether it gave any indication of any testing having been carried out by the inventors. To this, Dr Gallagher responded as follows:

> "*No....there's nothing in here to indicate that any testing was done. And if it was done, they didn't report any of the results. So, my only reaction would be, okay, well, they know what they should do, but it doesn't look like they've done it yet.*"

875. Asked whether he viewed the (a)-(g) list as being specific to Factor Xa inhibitors, Dr Gallagher indicated that he did not, that he saw this as "*a pretty general list*", continuing:

> "*As my career moved along and I stopped being an antithrombotics pharmacologist for a living and moved into team leadership project management, these were the kinds of things that we would use when we were orientating people to...when you develop a drug, here are the things you have to think about. So, it's a fairly general list*".

13. Attractiveness of Apixaban

876. Counsel for Teva put it to Dr Gallagher that Dr Taft (a witness for BMS whose evidence is considered later below) has indicated that he would understand the disclosures in p.6 of the patent application to give a skilled team, or a skilled pharmacokineticist, a reason to believe that apixaban has the desired profile and that the desired profile for the specific Factor Xa inhibitor is detailed in page 6. Asked what his view was of this, Dr Gallagher responded as follows:

> "[M]*y instructions were the priority date is 2001. As far as I know...the term 'apixaban' wouldn't be appropriate in 2001, because I don't think it existed yet. So, it seems like there's an element of hindsight there....*[As to p.6 offering] *a profile of a particular compound, it is a list of attributes for almost any compound, things that you would have to establish to determine whether or not it was good, not necessarily just as an antithrombotic, but for any of kind of a drug. And...when we had profiles and*

they had most of those kind of attributes, it wasn't a profile until there were...actual values to say 'This is why we think that it has the appropriate property, because such-and-such is such-and-such'. So, I have difficulty accepting the way Dr. Taft put it."

877. Pressed as to whether he agreed with the *substance* of Dr Taft's evidence (being that it is possible to discern a specific profile for a particular inhibitor of Factor Xa from p.6), Dr Gallagher indicated that he did not, stating as follows:

"*The list of attributes are the things...development teams, perhaps driven by a pharmacologist or by a biologist for the team...would have to do....*[S]*o, it's a fairly complete list. It leaves out toxicology, it leaves out some medical stuff and safety things. But...it would only describe a particular drug if there were values, data, results of tests that told you how well or how not well its half-life was or its oral bioavailability – the things we talked about yesterday. In the absence of results or data, it's just a list of attributes that you have to test for.*"

14. Utility

878. Moving forward to p.168 of the 652 application (the 'Utility' section), counsel for Teva drew Dr Gallagher's especial attention to the statement on p.169 "*The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin*" and asked what that sentence would convey to Dr Gallagher as a pharmacologist reviewing the patent application. To this, Dr Gallagher responded as follows:

"*It would suggest to me that they had a fairly open mind as to what kind of an anticoagulant they were looking for. Using the word 'or' means, okay, maybe we'll find some Factor Xa inhibitors or maybe we'll find some Factor II thrombin inhibitors. So, in contrast to the lines that we looked right at the beginning which said 'especially Factor Xa inhibitors', that sort of emphasises the 'especially', because it's not just Factor Xa inhibitors. It was one of the things – these are the kinds of phrases that made me think that this project was relatively early on*".

879. Counsel for Teva asked Dr Gallagher to give his opinion on the following observation on p.170 of the patent application:

"*Compounds tested in the above assay are considered to be active if they exhibit a Ki of ≤ 10 μM. Preferred compounds of the present invention have Ki 's of ≤ 1 uM. More preferred compounds of the present invention have Ki's of ≤ 0.1 μM. Even more preferred compounds of the present invention have Ki's of ≤ 0.01 μM. Still more preferred compounds of the present invention have Ki's of≤ 0.001 μM. Using the methodology described above, a number of compounds of the present invention were found to exhibit Ki's of ≤ 10 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.*"

880. To this, Dr Gallagher responded as follows:

"[I]*f you start out with a lot of compounds and you don't want to have to do the whole testing routine on all of them, you want to narrow them down to the ones that are...in the ballpark....*[S]*o, a threshold of ten micromolar is a pretty reasonable threshold to...get to a group of compounds that you can deal with and work with. So...it is a threshold, it's a way of kind of narrowing down the possibilities. Ten micromolar would not qualify as an effective anticoagulant, particularly a Xa inhibitor, if the micromolar is higher than the concentration of the Km of the natural substrate prothrombin.*"

881. Noting that the application moves on to state that "*The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model*" (the type of model described by Dr Gallagher earlier in his evidence), counsel for Teva asked whether this passage told Dr Gallagher anything about that model/test in the context of the application. To this, Dr Gallagher responded that "*It's* [a]*...sort of high level description of that test....*[I]*t's a description of a test, from what I can tell,* [that] *they may not have used yet, because there are no results of any actual experiments reported.*"

882. Counsel for Teva next drew Dr Gallagher's attention to the sentence, at p.171 of the application, which reads, "*The compounds of the present invention may also be useful as inhibitors of serine proteases, notably human thrombin, Factor VIIa, Factor IXa, Factor XIa, urokinase, plasma kallikrein, and plasmin*." Counsel asked Dr Gallagher to give an opinion on this sentence and what Dr Gallagher's perspective of it would be as a pharmacologist reviewing this application. To this, Dr Gallagher responded as follows:

> "*That was one of the written elements of the application that convinced me even more strongly that this project was in early days...so early that even though they might really want to eventually get a Factor Xa inhibitor, they were open to the possibility of stumbling across other types of serine protease inhibitors that might produce one setting or another. That was the only way I can kind of rationalise why they would have stated that in an application purportedly focused on Xa. So...[it is] early days [and]...if the chemistry that's covered by the patent hits that target or that target, they might take advantage of it. That's the only reaction I could have.*"

883. Counsel for Teva next drew Dr Gallagher's attention to the sentence, on p.171 of the application, which states that "*Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates*". Invited to make comment as to whether one could derive from this observation that the patented invention was going to be effective as a Factor Xa inhibitor, the following exchange occurred:

Dr Gallagher:	...[T]*hat gets to the same point; in front of line may have been Xa, but if the thrombin inhibitor showed up, they would go after it. I don't know how else I can interpret it.*
Counsel:	...[I]*n 2001 would you have expected that an effective Xa inhibitor could also be an inhibitor of urokinase, plasma kallikrein and plasmin, for example?*
Dr Gallagher:	*It's possible. One of the things we've talked about quite a bit is the importance of establishing selectivity; you're going after a new target and you don't want to hit other types of serine proteases. But because they are serine proteases, the compounds, the proteins that are mentioned here, it's not inconceivable that in the search for an inhibitor of serine protease X, they might stumble across one for serine protease Y....*
Counsel:	...[W]*ould you expect that also to be an effect of a Factor Xa inhibitor for the purposes of the patent?*
Dr Gallagher:	*You'd have to prove it to me. At risk of reiteration....there would have to be testing done to demonstrate uniqueness, selectivity and potency.*
Counsel:	...[W]*hat would the approach have been to test the selectivity in 2001 if you had a reason to believe that an inhibitor could hit the serine proteases identified there?*
Dr Gallagher:	...[I]*t may be that different companies had different rules of thumb, but our rule of thumb was the difference should be at least a factor*

of 10 over 3, so a thousandfold difference....

Counsel: ...[M]*oving on through the patent application, there is a section of the application beginning on page 188 that runs on until page 298. Is that a section of a patent application that you, as a pharmacologist in 2001, would typically have read or had an interest in?*

Dr Gallagher: *Oh, the examples? No. That's chemistry.*

Counsel: *Would you be qualified to read and understand the synthesis of a compound, as described in that section of the patent application?*

Dr Gallagher: *No.*

Counsel: ...[W]*hat information could you, as a pharmacologist, get from those sections?*

Dr Gallagher: ...[N]*ot very much. I mean, this is chemistry stuff....*[L]*et's say there were two of us...the pharmacologist and the chemist....If there was something interesting there, it would be up to the chemist to figure it out. I'm not sure what I would get out of these synthetic schemes.*

Counsel: ...[F]*rom your perspective is there anything in the synthesis section of the patent application that teaches you anything important about any one of the 140 compounds that are dealt with there?*

Dr Gallagher: *You have to remember, as a pharmacologist the things I'm looking for are things like Ki patterns, how potent is this compound, or not potent as the case may be, or perhaps how selective it is. A pharmacologist is a science guy looking for test results and pharmacology is the activity of these chemicals in various settings. And that's what I would have been looking for. But as far as I know, there isn't any of that information in here....From the standpoint of pharmacology, I can't get anything out of this.*"

15. Synthesis

884. Counsel for Teva drew Dr Gallagher's attention to the segment in Prof. Morrissey's first witness statement (para.88) where Prof. Morrissey states that it had been shown to him that 3.07g of the compound in Example 18 was synthesised, then continued "Yo*u say this was not something that you noticed from reading WO652, nor do you think this information would've been important to an skilled pharmacologist.*" To this, Dr Gallagher responded "[T]*hat's correct. There's no data there*" and affirmed the view that he had stated in his second witness statement to the effect that:

> "*Professor Morrissey continues in paragraph 88 to state that 3.07g would have been more than enough compound to run animal studies, including an AV shunt model. I agree that this quantity might have been sufficient for some testing. The amount of testing that would have been possible would depend on the biological properties of the compound including potency and selectivity. Therefore it is not possible to know what the extent of the testing might have been and the skilled person would need further information that is not in W0652 to determine the same.*"

C. Cross-Examination

1. Biochemist versus Medicinal Chemist

885. Counsel for BMS observed that in his first report Dr Gallagher describes how "*a pharmacologist worked with medical chemists to design and synthesise the compounds*", noted that he had referred both to 'biochemists' and to 'medicinal chemists', and asked whether he meant the same thing in using these terms. Dr Gallagher indicated that he did not. He was then asked by counsel for BMS to explain the difference and did so in the following terms:

"*Well, a medicinal chemist...in my setting, they were all organic chemists....*[T]*heir big job was designing and synthesising different compounds...that potentially could be used in settings like that. A biochemist is when you're also dealing with organic chemistry, but how it interacts in biological systems.*"

886. Counsel for BMS then drew Dr Gallagher's attention to para.5.5 of Dr Gallagher's initial report, where he states:

"*Having looked at WO131 and WO652 I think they were primarily directed at a medicinal chemist and pharmacologist ('Skilled Person' or 'skilled pharmacologist') and these are the disciplines that I think make up the skilled team ('Skilled Team'). I do not think that there is information or data in WO131 and WO652 which is directed to the later elements of the development process such as toxicology, pharmacokinetics, clinical studies, regulatory interactions, or marketing.*"

887. After affording Dr Gallagher the opportunity to re-read this paragraph, counsel for BMS noted that in it Dr Gallagher mentions pharmacologists and medicinal chemists but not biochemists and suggested that the reason for this is that biochemists are not actually involved in the drug design process, they are involved later. To this, Dr Gallagher responded as follows:

"*I have to speak from my own experience...*[I]*t may be different in different organisations....*[W]*hat would we would call early stage discovery, which was coming up with chemical candidates, which required a certain amount of testing, the testing was usually done by the pharmacology department, my department. And the actual biochemical evaluations of enzyme kinetics and, you know, what are the on rates and off rates of the inhibitor, that was the sort of thing that probably would have been done later. But it wasn't crucial at this point, the early stage.*"

2. Drug Design as a Repetitive Process

888. Asked by counsel whether he (Dr Gallagher) agreed that when it comes to drug design (i) the vast bulk of work done by the team of medicinal chemists and pharmacologists leads to a dead end, and that (ii) "*basically, you have to start again...educated by the previous failure or failures....You know what doesn't work and you may get some information about the direction to move in from the way that the compounds you have synthesised fail*", Dr Gallagher agreed with both propositions. I cannot but note that the 'dead end' point seems rather to point to the need for data, a point which seems to run counter to the wider case posited by BMS.

3. Common General Knowledge Document

889. Asked whether he agreed with the agreed CGK document, Dr Gallagher indicated that he was content with the portions of the document that relate to his particular expertise and that he would be content for me to use the agreed CGK document as a guide to the relevant common general knowledge.

4. The Coagulation Cascade

890. Asked whether he was satisfied for me to rely on the description of the coagulation cascade in the common general knowledge document and on the coagulation cascade schematic diagram that appears therein, Dr Gallagher indicated that he was so satisfied.

5. Anticoagulation

891. Dr Gallagher agreed with counsel for BMS that warfarin was the only orally administrable

anticoagulant available at the priority date of the patent in suit, that it is a very effective drug but suffered from certain deficiencies identified, amongst other places, at §6.18.4 of Dr Gallagher's report (and which are also touched upon in the agreed CGK document. These deficiencies include, *e.g.*, (i) slow onset/offset of action, (ii) risks of intercranial haemorrhage, (iii) the fact that its effect is impacted by diet and alcohol consumption, (iv) the fact that dosage requires constant monitoring, and the risk of drug-to-drug interactions. These known deficiencies, counsel posited, meant that "*by the priority date there was a clear clinical need to find an effective oral coagulant replacement*". Dr Gallagher agreed that this is so (and in fact this accords with the agreed CGK document).

892. Dr Gallagher also agreed, when it was put to him by counsel, that "*at...the priority date, thrombin and Factor Xa had been identified as the best potential products for the therapy*".

893. Dr Gallagher agreed when counsel for BMS put it to him that (i) there were at least two reasons why Factor Xa was identified as a good target, these being (I) it lies right at the heart of the coagulation cascade (so it is always involved) and (II) it only has antithrombotic effects, *i.e.* it is a one-action enzyme, (ii) although thrombin was an initial target, it was perceived to present with potential drawbacks *vis-à-vis* Factor Xa because (as noted in the agreed CGK document) "*thrombin has a more complex role, which includes both pro- and anti-thrombotic effects and it's, therefore, more difficult to ensure that you only achieve a desirable effec*t". Dr Gallagher also agreed that a further advantage of Factor Xa is that it has an amplified effect on thrombin production, albeit that the number of molecules catalysed at any one time is variable.

894. Counsel for BMS posited that the attractions of Factor Xa were such that "*virtually the entire pharmaceutical industry was engaged in a vigorous search for a Factor Xa inhibitor which could be orally administered*". Dr Gallagher agreed that with the exception of some companies (which was working on thrombin inhibitors) "*most companies were working on* [Factor] *Xa by 2001.*"

6. The Leadley Paper
(Leadley, Robert J., Jr, "Coagulation Factor Xa Inhibition: Biological Background and Rationale" (2001) 1 *Current Topics in Medicinal Chemistry* 151-159)

895. Counsel for BMS brought Dr Gallagher to the Leadley paper, a paper that identifies that there are a number of very good reasons for targeting Factor Xa. The exchange between counsel and Dr Gallagher at this juncture included the following:

Dr Gallagher:	...[T]*his was an important paper in 2001, laying out the state of play for Xa....*
Counsel:	...[W]*ould it be fair to say that...*[Leadley's] *discussion reflects...reasonably accurately the thinking of those working in the field at the time?*
Dr Gallagher:	*Yes....*
Counsel	*....And that thinking leads to the conclusion that it is targeting Factor Xa, which is responsible for the difference observed, rather than the specific properties of particular inhibitors?*
Dr Gallagher	....[A]*nd the common element was inhibition of Factor Xa. Is that the point?*
Counsel:	*That is correct.*
Dr Gallagher:	*Yes....*
Counsel:	*... Overall, the take-home message is that Factor Xa is what the drug developers should be looking at?*
Dr Gallagher:	*That's correct.*

7. The Betz Paper
(Betz, Andreas, "Recent Advances in Factor Xa Inhibitors"
(2001) 11(6) *Expert Opin. Ther. Patents* 1007-1017).

896. Counsel for BMS brought Dr Gallagher to the Betz paper, a paper that reviews a number of patent applications that had resulted from research in which researchers went looking for inhibitors with the required level of potency. The exchange between counsel and Dr Gallagher at this juncture included the following:

Counsel: *...It would be fair to describe this paper as being one addressed primarily to medicinal chemists?*

Dr Gallagher: *When there's lots of structures, that's usually the safest thing to assume....And there's lots of structures. So, yes, you're probably correct....*

[Warfarin and Apixaban]

Counsel: ...[T]*he need for an effective and safer therapy than warfarin was acute and the rewards for getting there would be very substantial?*

Dr Gallagher: *Yes....*

Counsel: *And on that topic, it would be fair to say that apixaban is that therapy and has been very successful, hasn't it?*

Dr Gallagher: *Are we sticking to 2001?*

Counsel: *No, since. I'm looking at the solution rather than the problem.*

Dr Gallagher: *...Yes, apixaban's a very good drug, I have to admit that. But in 2001, I would not have known about it.*

Counsel: *That's absolutely fine....*

[DX9065a]

Counsel: ...[A]*s he* [Leadley] *explains, extensive empirical studies show that inhibitors consisting of two basic moieties linked by appropriate spacers have been demonstrated to be the most potent. And he identifies DX9065a as exemplifying that approach, doesn't he?*

Dr Gallagher: *...Well, we actually synthesised, at Parke-Davis when I was working there, some of the DX compound....*[w]*e didn't really think that was that good an inhibitor.*

Counsel ...[H]*e says...'DX9065a...provides a useful lead for future inhibitors', that's how you viewed it?*

Dr Gallagher: ...[T]*hat's right. This was going in the right direction.*

Counsel: *And he indicates in the immediately following text that one of the things that everybody was trying to do was reduce the basicity of the binding groups in order to improve oral bioavailability....*

Dr Gallagher: ...[T]*his is really getting into medicinal chemistry land....I'm not that...comfortable, as a pharmacologist, interpreting this...information.*

[Potency and Selectivity]

Counsel: *Okay...can we then look at the potency and selectivity issues...which he deals with at the bottom of* [p.1015 of the article]..?

Dr Gallagher: [considers article] *Yes....well...that's the kind of Ki values we were looking for. It says nanomolar or picomolar. Picomolar is 10 to the minus 12, nanomolar is 10 to the minus 9. So, that's the range*

that most of us were looking for, yes.

Counsel: ...[I]*t was well known that that was the level of potency that was desirable?*

Dr Gallagher: *Correct....*

Counsel: *It would follow from that, would it not, that in the patent applications which are reviewed in this* [period]*...they will have resulted from work in which the researchers went looking for compounds which were capable of binding with the required level of potency; that must be right, mustn't it?*

Dr Gallagher: *Yes.*

Counsel: *There'd be no point in doing the research otherwise?*

Dr Gallagher: *Correct.*

897. It is important to note what is not being said in the last segment of the above-quoted exchange. The point being put to Dr Gallagher in this regard is not that, despite the absence of data, Betz identified a plausible therapeutic candidate from the patents. The point being put to him is that the work underlying the patents would have resulted from people looking for nanomolar compounds. That is wholly uncontroversial: after all, the whole field was looking for nanomolar compounds.

8. The 652 Application

i. Title and Expectations

898. Counsel began his consideration of the 652 Application by drawing Dr Gallagher's attention to its title, *viz*. "*Lactam-containing compounds and derivatives thereof as Factor Xa inhibitors*". Having done so, the following exchange occurred:

Counsel: *...Does that* [title] *give you just a little hint, perhaps, of what they're aiming at?*

Dr Gallagher: *Yes. Which is why, when I read the title, that I thought this would describe the project of identifying a Factor Xa inhibitor.*

Counsel: *And would it be fair to say that you didn't find anything in the document to suggest that they were trying to do anything else?*

Dr Gallagher: *...What it seemed to me, based on some of the writing, the text in the 'Utility' section was that they were ready and open, if they stumbled across something that was an effective, perhaps effective inhibitor of a serine protease other than Factor Xa, they might want to pursue it. That was one of the reasons that I mentioned that I thought 'Oh, this must be early days in this project'...*

Counsel: *So, basically, I don't think there's anything between us, in the sense that you are looking at this and saying they might find something with another utility and they were open to that possibility.*

Dr Gallagher: *That was the impression...I took away.*

ii. Activity and Testing

899. Counsel noted where in the patent the levels of potency are given in descending order and then the following exchange occurred:

[Structure of Patents]

Counsel: *...You're familiar with the way patents are written, aren't you?*

Dr Gallagher: *...I am not really familiar with it.*

Counsel: *...In that case, let me explain something to you, because it may*

assist your understanding of the document. It is normal when...a patent attorney is drafting a patent specification to put increasing levels of requirement for the claimed property. So 'I'd like ten of these, ideally I'd like 20, even more ideally I'd like 30, even more ideally still I'd like 40'. Do you see what I'm getting at?

Dr Gallagher: *Yes, I see.*

Counsel: ...[W]*hat that tells you, Dr Gallagher, is that the target they're really aiming at is the still more preferred target. Do you understand what I'm getting at?*

Dr Gallagher: *Yes. That's what they were aspiring to find.*

Counsel: *Yes. And the still more preferred target in this text is 0.001 micromolar.*

Dr Gallagher: *Right. One nanomolar.*

Counsel: *One nanomolar. Which is the sort of level that the industry was looking for.*

Dr Gallagher: *Correct.*

[Testing]

Counsel: *...I think you said in your oral evidence-in-chief that you couldn't see any evidence that they'd done any testing?*

Dr Gallagher: ....[P]*erhaps I should clarify. In the patent application it's pointed out that some Ki determinations were done and they found some compounds that met a threshold of ten micromolar Ki or less. That was for both Factor Xa and for thrombin. That is the only testing that I identified as having been done and reported in the application.*

Counsel: *So, you accept that the specification does say that they've done some testing?*

Dr Gallagher: *That they have done some testing, yes.*

[Potency]

Counsel: ...[W]*orkers in the field knew that ten micromolar potency was just a screening level?*

Dr Gallagher: *...I would say that that was the consensus view, yes.*

Counsel: *And they also knew that nanomolar potency, or something close to it - I think you said possibly even better was needed if a molecule was to be...potentially effective –*

Dr Gallagher: *...That also was the consensus view. High potency was the target.*

Counsel: *And that is knowledge that the reader of this specification brings with them when reviewing the document, isn't it?*

Dr Gallagher: *Yes.*

Counsel: ...[C]*an I put to you that if a skilled medical chemist, looking at the specification, concluded that there were indications...that some of the compounds might have high potency, as a pharmacologist you would consider that it was worth testing them to determine their potency and selectivity?*

Dr Gallagher: *Correct.*

Counsel: *And that if you did so and identified a compound from the specification which was potent and selective, it would be worth taking forward for further testing and evaluation?*

Dr Gallagher: *That's correct also.*

[Synthesis of Example 18]

Counsel:	*Can I just ask you...about the amount of Example 18 that was synthesised? I think I understood you to say in your oral evidence-in-chief that you didn't really read the worked examples, because they're addressed to the medicinal chemist and not to the pharmacologist?*
Dr Gallagher:	*That's correct.*
Counsel:	*And that would provide reason why you didn't notice the amount of Example 18 was being synthesised, because you didn't actually look for it?*
Dr Gallagher:	*That's correct. It had to be brought to my attention.*
Counsel:	*...If you had noticed it, you would've realised that Example 18 had been synthesised in considerably greater quantities than any other example, wouldn't you?*
Dr Gallagher:	...[T]*hat actually had to be brought to my attention too. Because there's 140 examples and I didn't immediately compare the amount made for Example 18 with the other examples.*
Counsel:	*Once it was brought to your attention, you've* [*sic* – 'you'd have'?] *realised that it was the case?*
Dr Gallagher:	*Yes, they made more of that particular compound.*
Counsel:	*...Assuming you had been given the data that showed that...*[Example 18] *was potent and selective, if you had notice*[d] *the amount of Example 18 which had been made, you would agree that it is sufficient to conduct the initial ex vivo and in vivo animal testing required to assess a material's basic pharmacological qualities?*
Dr Gallagher:	...[I]*t would support some testing. But the testing...depends on...the model you're doing and also...how...potent and selective it was. So, could some things be done with that quantity, three plus grams? Yes, probably. But it would certainly help me to know how potent and how selective and some other characteristics regarding solubility, for example.*
Counsel:	...[T]*hat would be useful data to tell you whether it was worth taking on board?*
Dr Gallagher:	*Yes...*

D. Re-Examination

1. The Betz Paper
(Betz, Andreas, "Recent Advances in Factor Xa Inhibitors"
(2001) 11(6) *Expert Opin. Ther. Patents* 1007-1017)

900. Counsel for Teva brought Dr Gallagher to p.1013 of the Betz article and, amongst other matters, to the observation therein that "*without data on biological properties of the protected compounds it is difficult to assess this patent's impact on the field.*" She then queried whether the Betz article undermines the evidence that Dr Gallagher gave in direct examination in relation to the need for biological data. To this, Dr Gallagher responded, "*I don't think so. I hope not.*"

2. The Light and Guilford Article
(Light, David and William Guilford, "Discovery of the Factor Xa Inhibitor, ZK 807834 (CI-1031)" (2001) *Current Topics in Medicinal Chemistry* 121-136)

901. Counsel for Teva brought Dr Gallagher to Table 13 of the Light and Guilford article and asked

whether the said table gives the kind of potency data that would be of assistance to Dr Gallagher as a pharmacologist. Dr Gallagher indicated that this was precisely the kind of information that he would be looking for.

902. Counsel then brought Dr Gallagher to Table 15 in the same article, "*just* [to] *confirm whether that's the kind of data, as a pharmacologist, you would expect to receive to be able to assess whether a compound is likely to be effective*". Dr Gallagher again indicated that "*precisely this is the kind of information I'd be looking for.*"

3. The 652 Application

903. Counsel brought Dr Gallagher to the synthesis section of the patent application (at p.272), noted that line 7 indicates that 424 mg of this compound had been synthesised and asked "[I]*f you were to assume that you were told that this compound had very low nanomolar potency...and a thousandfold selectivity over thrombin and the other serine proteases in the fibronolytic pathway, would you believe there's a good basis to continue with testing that compound?*" Dr Gallagher responded, "*Yes, if that information was available, absolutely.*"

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The Evidence of Professor Morrissey

904. Unfortunately, Prof. Morrissey fell unwell during the course of the proceedings and, as a consequence, was not called to the witness-box. The parties have agreed between them that Prof. Morrissey's written evidence can be admitted without his being cross-examined on condition that: (i) the transcript of Prof. Morrissey's evidence in England is also accepted as part of his evidence for the purpose of these proceedings; (ii) the agreed CGK document is accepted and agreed as part of that evidence; and (iii) Teva is not to be taken as conceding or foregoing any point or waiving or qualifying its right to make any relevant submission or argument. Subject to para.4 of this judgment, an abridged version of the text of Prof. Morrissey's witness statements is set out at Appendix 9. The transcript of his evidence in England is set out at Appendix 20. I respectfully invite readers of this judgment to read those appendices and then proceed to the next chapter.

X. THE PHARMACOKINETIC EVIDENCE

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The Evidence of Dr Wargin

A. Introduction

905. Dr Wargin is a distinguished pharmacokineticist whose résumé includes a period as an assistant professor at the University of North Carolina at Chapel Hill and a lengthy career in the pharmaceutical industry, during which he focused on early-stage drug development including in vitro pharmacokinetic/absorption, distribution, metabolism and excretion studies, in vivo pharmacokinetic studies and the toxicokinetic components of drug safety studies in animals, and more particularly components of drug safety in animals that are conducted for a USA Investigational New Drug. He has worked in the area of pharmacokinetics for approximately 40 years. Subject to para.4 of this judgment, the text of Dr Wargin's witness statements is set out at Appendix 15. I respectfully invite readers of this judgment to read that appendix and then return to this chapter.

B. Examination

1. Skilled Person and CGK

906. Counsel for Teva noted the definition in Dr Wargin's first witness statement of a person skilled in the art (being a person skilled in the art to whom a patent is addressed and who would have a practical interest in the subject matter of the patent; she may be a member of a skilled team, is uninventive, but has CGK in the relevant field). Counsel then asked if that was Dr Wargin's understanding of the role that he was discharging: giving evidence as a skilled person for the purpose of that definition. Dr Wargin indicated that this was his understanding. He also confirmed that the relevant time as regards the evidence he was giving was 17th September 2001.

907. In response to counsel, Dr Wargin confirmed that paras.131-164 of the agreed CGK document represent his understanding as to the common general knowledge of a pharmacokineticist in these proceedings.

908. Turning to the agreed CGK document and responding to questions from counsel for Teva, Dr Wargin indicated that:

- the acronym ADME deployed in the CGK stands for 'absorption', 'distribution', 'metabolism' and 'excretion', being "*the important processes that determine the pharmacokinetics of a drug*";
- the term "*absorption*" is:

> "*an indication of the rate and extent of the availability of the drug to the site of action. For example, if the site of action is in the plasma, it's an indication of the rate and extent of the appearance of drug in the plasma. And from that, depending upon on how high the concentration gets and when that concentration peak occurs, we can get an understanding of how quickly the drug can be absorbed.*"

- he is satisfied for me to proceed on the concept of "*absorption*", as outlined in the agreed CGK document.
- the term "*distribution*" has the following meaning when it comes to the development of a drug:

> "[W]*hen a drug is administered into the stomach circulation, we have a knowledge of the dose of the drug that's been administered to the body. And ...in order to do any pharmacokinetic analysis, we need to have concentrations of the drug, in this case in the blood, in the plasma....*[T]*o do that, we have to have methods to measure those concentrations. And so those have to be developed and validated. And so that's an important factor to consider. Because in order to calculate the volume and distribution, we have to know the dose administered and the plasma concentration that we observed in the plasma. And that ratio gives us a measure of the volume of distribution. Normally, the volumes of distribution are measured or calculated, expressed in litres, a volume. And the volumes can potentially range from small volumes, like a drug that only distributes into the blood, to very large volumes that are actually not true volumes, but if blood concentrates in, let's say, fatty tissue, we could have a volume of distribution that's calculated to be, say, 1,000 litres. So, it's often not an anatomical or physiological space that volume distribution gives us.*"

– the definition of "*distribution*" in the agreed CGK document accords with his understanding of that term.
– as regards the observation in the agreed CGK document (§148) that "[D]*etermining V_D requires in vivo experiments. Key factors which affect V_D are.... how hydrophilic or lipophilic a compound is. Compounds which are hydrophilic tend to have a low V_D and are therefore more likely to be retained in the blood*" (with the shorthand 'V_D' referring to the 'volume of distribution') and by way of explanation:

> "[G]*etting back to the example about the volume of distribution, a hydrophilic substance is a water-loving substance and so it'll tend to stay in the blood compartment, whereas a lipophilic substance is a fat-loving substance, and so in that case we would see these large volume distributions that I was talking about, because blood distributes out of the blood compartment into the tissue compartment....A low volume of distribution most likely would be a value that could be equal to blood volume or it could be equal to total water volume. So, we're talking maybe eight litres to 30 or 40 litres. We consider it a very low volume of distribution. ....[I]n the case...of a Factor Xa, that will take place in the blood compartment....we'd like to have the blood retained in the blood compartment*."

– when it comes to the concept of a drug's half-life:

> "*half life is a very important parameter in pharmacokinetics, because it gives...an idea of how long the effects will last. And for most drugs, they are eliminated from the body by a first order process, meaning that it's an exponential decay. And the half life then is measured as, or usually we estimate half lives as the time it takes to decrease the concentration by 50%. So, if we start at 100, one half life is 50%, the second one would be 25% of the remaining drug. So, it takes about five half lives for the drug to be about 97% eliminated. The longer the half life, of course, the longer the drug will remain in the body.*"

– the analysis of drug half life in the agreed CGK document accords with Dr Wargin's professional experience.

– the equation concerning half-life outlined at §152 of the agreed CGK document is part of the common general knowledge.

– by way of explanation of the concepts of 'metabolism' and 'excretion':

> "*So, metabolism; basically, once a drug is absorbed, the body has a number of enzymes that can metabolise, meaning change the structure of the drug and make it more readily eliminated from the body. Because the body will treat drugs as foreign substances in many cases....*[T]*he enzymes that are primarily responsible for metabolism are called cytochrome P450s. And there are about maybe ten very common cytochrome P450s. And we all have various amounts of these enzymes. And they're primarily located in our liver, but also in the wall of our gastrointestinal tract....*[W]*hen a drug is administered, it's possible that some of the drug is metabolised by those enzymes in the gut wall and then when the drug is absorbed into the liver then there's potential for more metabolism. The most common enzyme, P450 enzyme, is called 3A4, cytochrome P450 3A4. And most of us have large amounts of 3A4 and we can metabolise many drugs – many drugs are called substrates for 3A4 and they're readily metabolised. There are other enzymes that are present in lower amounts and some are called polymorphic enzymes, meaning some of us have low amounts and some higher. So, the amount of time that a drug remains in the body is variable, depending upon the subject and very dependant, if the drug is metabolised, very dependent on the presence, the location and the amount of these enzymes*
>
> ...
>
> [E]*xcretion...is another process. So, most drugs are metabolised or excreted by the kidneys. So, in some cases some drugs may be 100% metabolised with very minimal excretion by the kidneys; other drugs, perhaps 50 or 60% could be excreted by the kidneys. And when that happens, it's important, we have to understand the kidney function, the renal function of a patient. Because if a parent's renal function is somehow impaired then the drug will have a longer half life and it could lead to problems*".

– the definition of metabolism and excretion outlined at §179 of the agreed CGK document accords with Dr Wargin's understanding of those terms.

– as to 'solubility' and its relevance to drug development, "*for a drug to be absorbed, it has to be in solution in the GI tract. So, if a drug is given orally, it'll typically be given, say, as a tablet, and that tablet would have to disintegrate into particles and then dissolve into a solution and it's absorbed after it's dissolved.*"

– as to the concept of 'pharmacokinetic profile', "*a pharmacokinetic profile consists of deriving or calculating all of the various pharmacokinetic parameters – the ones we've talked about so far would the half life and the*

volume of distribution. But there are others. We talked about metabolism and excretion. And those two processes make up, they influence the clearance of the drug. And the clearance of the drugs tells us how much of a volume of plasma from which a drug can be removed in a given time period."

– as to the concept of a 'clearance parameter', "*a really important part of the pharmacokinetic profile...we usually...*[express]*...that in units of litres, so a volume from which the drug is removed in a period of time, say* [an] *hour. So, the units on clearance are litres per hour. And a drug with a very low clearance can accumulate very high concentrations of drugs; a drug with high clearance concentrations would be lower.*"

2. Pharmacokinetic Profile and Qualities

909. Asked whether (i) a pharmacokinetic profile will include units and figures, and (ii) whether pharmacokinetic qualities are an important determinant of candidate selection, Dr Wargin gave an affirmative answer to both questions.

3. ADME Data Needed at Early Stage of Drug Development

910. Asked what his view would be of the proposition that ADME data are things you need at an early stage of a drug development programme, Dr Wargin indicated that "*they would be needed very early in development*".

4. Patent Application 652 of Interest to Skilled Pharmacokineticist?

911. Asked whether patent application 652 "*would...be of interest to a skilled pharmacokineticist*", Dr Wargin indicated that "*potentially it would be*". Asked whether he had found anything of interest to him therein in the capacity of skilled pharmacokineticist, Dr Wargin indicated that "*most of the document consists of material that would be interesting to medicinal chemists. And that's not an area that I have expertise in. But there would be sections, and are sections, say in 'Utility' and...other areas that would be of interest to a pharmacokineticist.*"

912. Having reminded Dr Wargin of the definition of a 'skilled person' for the purpose of the present proceedings (in particular the notion of a 'skilled person' as a person with a practical interest in the subject-matter of the invention), counsel for Teva asked whether the patent application would be something that Dr Wargin, as a pharmacokineticist, would have a practical interest in, *i.e.* is it something that he considers would be directed to a pharmacokineticist? To this question, Dr Wargin responded that "[W]*hen I picked up the document, I was...hoping that I'd find pharmacokinetic information. And there are some...pharmacokinetic concepts expressed in the document, but...there's...very few...pharmacokinetic facts.*"

913. Brought to p.6 of the application and invited to comment, Dr Wargin observed as follows:

"[T]*hese* [are]*...concepts and all of them are important. We've talked about solubility...clearance,* [and] *the volume of distribution. We've not talked about protein binding, that's another factor. And we talked about cytochrome P450s. So, all of these would be important theoretical concepts for a pharmacokineticist....*[W]*hen I worked at Glaxo Wellcome, I spent a couple of years in project management...looking across...the whole piece of drug development. And one of the things that we always did before we went through the exercise of developing a drug was develop what we called the target product profile. And that was a list of attributes that we would hope, at the end of the day, would provide us with a valuable medicine. And we had individuals on a project team from all disciplines in the company involved in developing target product profiles. So, this is the kind of thing, these activities on*

page 6, these would be more or less the pharmacokinetic target profile that we'd like to see, we would be including all of these....[all of which] *would be CGK.*"

914. Asked whether he could see anything on p.6 (in sub-paras (a)-(g)) referable to any particular compound or target, Dr Wargin mentioned serine proteases, Factor Xa inhibitors, and the notion of limited CNS penetration ("*that's the whole concept of wanting to keep the drug in the central compartment*").

915. Asked whether he agreed with Dr Taft that p.6 presents "*a pharmacokinetic profile for a specific compound*", Dr Wargin indicated that:

> "[T]*his profile would apply to any drug that is primarily designed for activity in the central compartment. And the thing that gives this away is limited CNS penetration....*[S]*o there's a little bit of specificity here, but not very much....[I]t doesn't explain specifics about what is desired. For example, let's just pick protein binding...it doesn't explain whether we're looking for a drug that has low protein binding or high protein binding. So, there's just not enough specificity...I guess.*"

5. Dosage

916. Turning to p.182 of the patent application and the mention therein "*that a possible range of doses could be from 0.001 to 1,000mg/kg*" and recalling the observation at §7.1.6 of Dr Wargin's first statement, that "*The skilled pharmacokineticist would recognize that this range would provide a fixed dose upper of 70,000 mg for a 70 kg patient. This would be 70 grams per dose and the proposed 100 mg dosage form would require each dose to consist of 700 capsules*", and having invited Dr Wargin to make comment the following exchange ensued between counsel and Dr Wargin:

Dr Wargin:	...[T]*his is a pretty unrealistic situation. I think this dosage range, 0.001 to 1,000mg/kg would probably cover the doses of all drugs that have ever been developed or ever will be developed, because of this wide range. 70,000mg or 70g would be an impossible dose to be able to take. So, I would've expected some narrowing of that range. And they do narrow it to preferably, and most preferably, lower doses, but there's just no specificity about the doses.*
Counsel:	*So, having just gone through those few parts of the patent application, I know you've read it previously, but you say at paragraph 4.7 of your statement that it contains too little relevant information or data with sufficient detail to permit the skilled pharmacokineticist with common general knowledge at the relevant date to conduct the necessary work. Can you explain that conclusion, please?*
Dr Wargin	....[T]*hroughout the patents there's very little specific information and really no pharmacokinetic data with which to assess the quality of the potential compounds.*

6. The Light and Guilford Article
(Light, David and William Guilford, "Discovery of the Factor Xa Inhibitor, ZK 807834 (CI-1031)" (2001) *Current Topics in Medicinal Chemistry* 121-136)

917. Turning to the Light and Guilford article and, in particular to Table 13 therein and the table on p.15, counsel invited Dr Wargin to give his view on the type of information set out thereat, Dr Wargin observed as follows:

> "*I looked at this paper and a couple of others in this timeframe....*[T]*his paper was*

published in 2001...in Current Topics in Medicinal Chemistry*, so it's a med-chem focused paper. And this is work that...was done at Burlex....looking at Factor Xa inhibitors and Table 13 actually has data...the Ki's that Dr Gallagher was talking about....But importantly from a pharmacokinetics point of view, they also have pharmacokinetic data....*[a]*nd the nice thing about that – we haven't really talked about bioavailability – but one of the problems with some of these Factor Xa inhibitors that were developed in this timeframe or a little earlier is, even though they were very potent, they had very poor bioavailability. So, you can't really develop a drug, even if it's very potent, you can't really develop a drug that has bioavailability, because not enough will get into the systemic circulation. And that was a problem with many of these drugs. And some companies...just never found a drug that had good enough pharmacokinetic properties. So, this is an example in Table 13 where they actually have data....*[T]*hey're providing the pharmacokineticist reading this paper with actual...pharmacokinetic data....And from this information, they can calculate what's called the absolute bioavailability of the drug, how much gets into the stomach circulation....And if they can get bioavailability at 40% or greater, that's a pretty good sign for a drug like this*."

7. Examples Section of Patent

918. Returning to the patent application (p.188), and the section headed *'Examples'*, counsel asked whether this was a section of a patent that would be of interest to a skilled pharmacokineticist? To this, Dr Wargin responded, "*Not really*".

8. Synthesis of Example 18

919. Referring to Dr Taft's statement and mention therein of the synthesis of a particular amount of Example 18, and invited to make comment, Dr Wargin indicated as follows:

"*So, Example 18 was – so, I read the patents and I didn't spend as much time, obviously, on the medicinal chemistry part...I was looking primarily at the pharmacology, but more importantly at the pharmacokinetics. So, I...did not pick up* [on] *the fact that they had synthesised 3.07g of Example 18. Which is not surprising, because there's a lot of details - six hundred and some pages. So, I did not pick that up, it had to be pointed out to me*."

920. Referring to §168 of the agreed CGK document and the statement there that "*The amount of material needed to perform an in vivo preclinical pharmacokinetic experiment depends on the goal of the experiment and the species of animal tested*", Dr Wargin confirmed that this was also his understanding, and agreed with Dr Gallagher's evidence (as recalled by counsel for Teva) "*that it would also depend on the biology of the compound in question, the potency, selectivity and so forth.*"

921. Counsel for Teva recalled that (i) "*Dr Taft, in his witness statement, has drawn certain conclusions from the fact that 3.07g of Example 18 were synthesised and he said this gives a positive reason, combined with the list on page 6, to believe that there was actually a positive reason to believe that apixaban had the desired pharmacokinetic profile of both the low volume of distribution and an even lower clearance*", (ii) in Dr Wargin's second witness statement (at §§1.12 and 1.13) he describes this as speculation and states that it is not credible, and asked (iii) whether there was anything further that Dr Wargin wanted to add or to say about Dr. Taft's position in this regard. Dr Wargin indicated that there was not.

922. Counsel for Teva queried whether there was anything, from Dr Wargin's perspective as a skilled pharmacokineticist, in the synthesis section of the patent application, that taught him that there was any reason to believe anything particular about one compound over another. To this, Dr Wargin responded as follows:

"*No, not necessarily. I mean, there were several compounds that were synthesised in, say, 500mg, for example, and that would...definitely be enough compound to do some of these screening tests, the in vitro screening tests, I imagine. So, it's not clear to me whether this was the only, because they synthesised so much, whether this was the only compound tested. It seems that that wouldn't be likely. But Dr Taft was pretty insistent that this was the molecule that would turn out to be the one. I think he brought it up five or six or seven times in his witness statement. But there are times when pharmaceutical companies synthesise fair amounts of drug* [because]*...say they want to use the particular molecule as a backup, or they may even just want to sue it as an internal standard for developing a bioanalytical assay, they may want to use it as a tool compound, the kind of thing that Dr Gallagher was talking about. So, I wouldn't say necessarily that just because a large amount was synthesised that that would necessarily mean that was the drug selected. And there's no evidence one way or another that they did anything*".

C. Cross-Examination

1. Some Acceptable Elements of Professor Taft's Report

923. Counsel for BMS noted that from §1.2 of Dr Wargin's second report, Dr Wargin essentially endorses §§38-60 of Prof Taft's first report and asked if Dr Wargin would be content for those paragraphs of Prof. Taft's report to be used to explain to me some of the detail around the nature and role of pharmacokinetics in drug development? Dr Wargin indicated that he "*most likely would, yes*".

2. Bioavailability

924. Dr Wargin agreed with the observation by counsel for BMS that "*pharmacokinetics is the study of the way in which the body deals with a drug and how it is absorbed, distributed in the body, metabolised and excreted*". Referring to the description of pharmacokinetic studies referred to at §§54-60 of Prof. Taft's first report, counsel for BMS suggested that those studies "*establish how much of a drug is absorbed into the body, where it is distributed and how long it remains active before being broken down and secreted*", and suggested that that was their purpose – to which Dr Wargin responded "*More or less, yes*."

925. Counsel for BMS noted that at §1.4 of Dr Wargin's second report he (Dr Wargin) indicates that he agrees with Prof. Taft's description of pharmacokinetic testing at §§61-66 of his report, and asked whether Dr Wargin would be content for those paragraphs of Prof. Taft's evidence to be used to explain some of the detail around the testing involved. Dr Wargin indicated that he would.

926. Counsel for BMS noted that at §§5.9-5.14 of his first report Dr Wargin discusses the properties desirable in a drug in order to be what Dr Wargin describes as a safe and effective medicine, and refers to desirability of high bioavailability . At this juncture the following exchange transpired between counsel for BMS and Dr Wargin:

Counsel:	...[O]*ne of the first things that you note is that it should have good high bioavailability.*
Dr Wargin:	*Yes, preferably high. 70% is definitely acceptable. Some drugs, some...effective approved drugs may only have 20% bioavailability. But generally, the higher the bioavailability the better.*
Counsel:	...[I]*deally you'd like 100%...*
Dr Wargin:	*Ideally....*
Counsel:	*Because that would be safe drugs....*[a]*nd I think you've explained*

that orally administered drugs have to pass through a gastrointestinal tract and be absorbed into the body without breaking down before they can be become available to act as active molecules?

Dr Wargin: *That's right.*

Counsel: *If only a small proportion of the drug is absorbed intact then a larger amount has to be administered orally to administer a therapeutically effective dose?*

Dr Wargin: *That's correct.*

Counsel: *And as you point out in 5.10, if a drug is sufficiently fully absorbed, there may be insufficient absorbed to achieve a therapeutic dose.*

Dr Wargin: *Correct*.

Counsel: *And that would make it not usable as an orally administrable medicine..?*

Dr Wargin: ...[T]*rue.*

Counsel: *So, oral bioavailability is one of the key tests...carried out by a pharmacokineticist when looking for oral medication?*

Dr Wargin: *That's right. That's one of the first things we do....*

Counsel: *It's entirely possible...for a candidate molecule for use as an inhibitor of an enzyme such as Factor Xa to show high potency and selectivity but to have such poor bioavailability that it would not be usable as an oral therapy?*

Dr Wargin: *Absolutely....*

Counsel: *And if such a molecule is found to have poor oral bioavailability, there's no point...taking it forward for further testing, is there?*

Dr Wargin: *Unless you decide that it would be acceptable to use it like an injectable....*

Counsel: *An intravenous treatment?*

Dr Wargin: *An intravenous drug....*

Counsel: *But if you're looking for a drug which will be administered orally, that's basically a stop point?*

Dr Wargin: *That's right, yeah.*

3. Variability

927. Counsel for BMS observed that Dr Wargin had pointed out that there may be variations in blood plasma concentration of a drug both in individual patients and between patients and asked if that is common. At this point, the following exchange occurred between Dr Wargin and counsel:

Dr Wargin: *Basically, it happens all the time....*[A]*ll drugs will be variable, depending upon patient characteristics....In pharmacokinetics, we call these covariates. And they can very much affect the variability of pharmacokinetics. And we look at two...we look at inter and intra subject variability. So, the variability between subjects is much higher than – like, your own variability would be...from day-to-day when you take drugs. So, variability is key.*

Counsel: . ..[Y]*ou've explained that you test for inter and intra patient variability; presumably you have to test lots of patients and take samples from them?*

Dr Wargin: *We do....*[Y]*ou may be aware that...*[when it comes to] *phases of drug development, there's really three....In the first...a small number of subjects, often healthy volunteers...*[T]*he second is subjects with a diseased state but not necessarily a huge number – we're looking for primarily for safety...*[P]*hase three is the big clinical trials where we're looking for...safety and efficacy....*[I]n

those trials we take, from a large number of subjects...a small number of blood samples....[F]*rom that information, we can determine how much intra subject variability is....*[T]*hen we can look at the sub-populations of those covariates and then we may have to design specific dosing regimens based on that variability.*

Counsel: *And there may be circumstances in which the variability between and within patients is so great that the material is unsuitable for use as an oral therapy because it's too difficult to control?*

Dr Wargin: *That's possible. But actually there's quite a few drugs with very high variability that are on the market....But there...are more issues sometimes with safety with that much variability.*

Counsel: *In those circumstances, the dose has to be very carefully tailored to the individual patients?*

Dr Wargin: *Yes*.

4. Half-Life

928. Turning next to the issue/importance of half-life, the following exchange took place between counsel for BMS and Dr Wargin:

Counsel: *Ideally, one is looking for a drug whose half life permits it to be administered daily and has a sufficient window, therapeutic window, to allow that to be done safely?*

Dr Wargin: *That's...the gold standard.*

Counsel: ...[I]*f the half life is too long or too short, there will be issues taking the drug forward as a candidate for continuous oral therapy, wouldn't there?*

Dr Wargin: *That's true.*

Counsel: *You've discussed clearance from the body and the impact that disease in various organs may have on this. Again, these are matters that need to be evaluated by testing?*

Dr Wargin: *That is correct. So, once we've established the pharmacokinetic profile in healthy volunteers, we would typically do additional studies in renal impaired and hepatic impaired patients potentially. So, clinical pharmacology in drug development is typically 10 to 20 studies, maybe more, in order to get a drug approved. There's a huge amount of clinical pharmacology that has to be done....*

Counsel: *An additional issue that you identify in 5.14 is drug interactions. Again this may lead to complications in administering a drug?*

Dr Wargin: *Absolutely.*

Counsel: *And it may be that the complications are such that they are so as to render its use impractical or so severely limited that it's not worth pursuing?*

Dr Wargin: *That is possible. But again, we have methods....tests that tell us whether or not a particular drug will inhibit the metabolism of other drugs....And if there is a potential interaction, we may have to do a clinical study assessing the possibility. So, there are ways around drug-drug interactions, but certainly the gold standard for a drug would be not to inhibit drug metabolism.*

5. Factors of Concern

929. When counsel suggested that failure in respect of one or more of the above-considered criteria is common in the drug development process, Dr Wargin indicated that this is possible, that there are lots of other reasons why drugs would fail "*but pharmacokinetics is sometimes the case*". At this point, the following exchange occurred between counsel for BMS and Dr Wargin:

Counsel:	*And....you certainly can't predict that a molecule will make an effective therapeutic agent simply because it is potent and selective?*
Dr Wargin:	*That's true.*
Counsel:	*On the other side of the coin is that in the search for an effective Factor Xa inhibitor, a molecule which is potent and selective would be of interest to take forward for further studies to which the pharmacokineticist would subject it?*
Counsel:	*Yes*".

6. Dosage

930. Counsel for BMS recalled his interaction with Dr Gallagher concerning how patent specifications are drafted. It will be recalled that the following exchange occurred between counsel for BMS and Dr Gallagher concerning how patents are written:

Counsel:	*...You're familiar with the way patents are written, aren't you?*
Dr Gallagher:	*...I am not really familiar with it.*
Counsel:	*...In that case, let me explain something to you, because it may assist your understanding of the document. It is normal when...a patent attorney is drafting a patent specification to put increasing levels of requirement for the claimed property. So 'I'd like ten of these, ideally I'd like 20, even more ideally I'd like 30, even more ideally still I'd like 40'. Do you see what I'm getting at?*
Dr Gallagher:	*Yes, I see.*
Counsel:	...[W]*hat that tells you, Dr Gallagher, is that the target they're really aiming at is the still more preferred target. Do you understand what I'm getting at?*
Dr Gallagher:	*Yes. That's what they were aspiring to find.*
Counsel:	*Yes. And the still more preferred target in this text is 0.001 micromolar.*
Dr Gallagher:	*Right. One nanomolar.*
Counsel:	*One nanomolar. Which is the sort of level that the industry was looking for.*
Dr Gallagher:	*Correct.*

931. Counsel for BMS then addressed the issue of dosage with Dr Wargin in the following terms:

Counsel:	....[Y]*ou heard what I said to* [Dr Gallagher]*...about how patent specifications are drafted? ....And* [how] *the narrow net is the one you're really aiming at?*
Dr Wargin:	*....Understood.*
Counsel:	*And that range, I think in a 70kg patient, 20mg per kg per day is a perfectly reasonable dose...isn't it?*
Dr Wargin:	*....I guess it's just a matter of seeing that first one. It just seems...totally unrealistic, but...I understand the rationale.*
Counsel:	*....You were asked some questions about the amount of Example 18 which was synthesised.*
Dr Wargin:	*Yes....*
Counsel:	*I think I understand you, like Dr. Gallagher, to say that bit of the*

specification is not really aimed at somebody like you, so you had to have all these facts pointed out to you?

Dr Wargin: *That's right....It would be really up to the medicinal chemists and the pharmacologists to bring on board pharmacokinetic or ADME expertise and share with them, say, the list of leads....[and] we'd want them to come to us with data to convince us and help us understand why they feel these are promising candidates. And then we would proceed to do the initial invitro studies....*

Counsel: *I think you said in your evidence-in-chief that half a gram would be more than sufficient to do the invitro studies?*

Dr Wargin: *Yes....*

Counsel: *And if you were provided with a material which you were told was...potent and selective, three grams would be more than enough to do the basic in vivo testing to assess the material's basic pharmacokinetic properties and its ADME?*

Dr Wargin: *That would be a stretch, I think. I guess it depends on the species....I doubt if three grams would be sufficient.*

Counsel: *Three grams would enable you to do initial pharmacokinetic testing, would it?*

Dr Wargin: *Initial invitro testing...limited in vivo testing.*

Counsel: *Limited in vivo testing?*

Dr Wargin: *Yes.*

D. Re-Examination

932. Counsel for Teva had no further questions for Dr Wargin.

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The Evidence of Professor Taft

A. Introduction

933. Professor Taft is a professor of pharmaceutics and has been doing research and teaching courses in pharmacokinetics at Long Island University, Brooklyn, for almost 30 years. Subject to para.4 of this judgment, an abridged version of Prof. Taft's written evidence is set out at Appendix 13. Subject to what I state in Part B of this chapter, I respectfully invite readers of this judgment to read that appendix and then resume reading here.

B. Some Difficulties With the Evidence of Professor Taft

934. Professor Taft is a learned and distinguished individual who proved to be a most engaging person when he gave his testimony in this case. However, in the particular context of the present proceedings his evidence presented with a number of difficulties. Rather than 're-invent the wheel' in this regard, I would simply (and respectfully) adopt the below-quoted observations in the closing written submissions of Teva:

> "*24. Professor Taft's reports were prepared in an unfortunate manner which fails to reveal three matters of material significance. First he had been instructed in Canada, where he learned the case was about apixaban before he turned to prepare his reports. Also in Canada he had taken into account as his primary reason on plausibility that apixaban was specifically claimed whereas that is not permissible in law in this jurisdiction....*
>
> *25. His report in England contained an express disclaimer that he had been informed not to have regard to the fact that apixaban is specifically claimed in the Patent....No such disclaimer was identified in his reports in these proceedings, nor did he mention that he was aware that the proceedings concerned apixaban before he came to submit his written or oral evidence here .....*
>
> *26. Second, Professor Taft agreed that he had never worked on anticoagulants or antithrombotics before the priority date...and explained that he had done a search of the literature to prepare his report....It is unfortunate that his reports do not disclose, nor could he remember, whether the articles cited in his reports were found during his literature search or otherwise supplied to him....*
>
> *27. Third Professor Taft gave evidence regarding the synthesised quantity of Example 18. He agreed that organic chemistry is not his "strong suit" and he would stay in his lane rather than enter the arena of medicinal chemistry....Further, he volunteered that he did not notice the amount of synthesised quantity of Example 18 when reading the Application but that this was probably pointed out by an attorney....He also accepted that he would not understand the detail of the synthesis exercise. However, he nonetheless maintained his evidence as to the significance to the synthesised amount of Example 18 and the mode of synthesis (despite having no relevant expertise to opine on same).*
>
> *28...* [W]*hereas in the UK he* [Prof. Taft] *made clear that this knowledge was derived from and contingent upon Dr Camp (BMS's medicinal chemist), that was absent in his evidence in these proceedings....*[So] *that evidence....is plainly based on the views of Dr Camp and not on anything known by Professor Taft himself.*"

935. Teva submitted in its closing oral submissions that Prof. Taft's evidence should be held to be

inadmissible. However, I do not see that I need to adjudicate on that submission. This is because, for the reasons identified elsewhere in this judgment, I respectfully do not accept that a skilled pharmacokineticist would be a member of the skilled team. Consequently, I have, in any event, had no real regard to the evidence of Prof. Taft or Dr Wargin in arriving at my judgment in these proceedings. That said, if only for the sake of any appellate court asked to adjudicate in these proceedings, I consider that it is incumbent upon me to identify what evidence was given by each of Dr Wargin and Prof. Taft and have done so, respectively in chapter 25 and below.

936. I emphasise that while the above particular difficulties present with Prof. Taft's evidence in these particular proceedings, I do not mean in any way to impugn his personal or professional achievements as a learned and distinguished scholar in pharmaceutics and pharmacokinetics.

C. Examination

1. Research Objectives

937. Counsel for BMS brought Prof. Taft to para.79 of his first witness statement, where Prof. Taft observes as follows:

> "*The vast majority of the rest of the Application describes the chemical structures and synthesis of a genus of lactam-containing factor Xa inhibitors. This would be of greater interest to the medicinal chemist on the skilled team than the pharmacokineticist. However, the skilled pharmacokineticist would have been particularly interested in the advanced research objectives listed on page 6 of the Application. The skilled pharmacokineticist would recognize, on the basis of these objectives, that the project had gone beyond merely identifying compounds that interacted with the target to identifying compounds with the desired pharmacological profile. The Application teaches that it was desirable to discover factor Xa inhibitors having advantageous and improved characteristics, in categories (a) to (f) in particular, which would have been understood by the skilled pharmacokineticist to include an overall sought-after pharmacokinetic profile:*
>
> > '*Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors. In addition, it is also desirable to find new compounds with improved pharmacological characteristics compared with known factor Xa inhibitors. For example, it is preferred to find new compounds with improved factor Xa inhibitory activity and selectivity for factor Xa versus other serine proteases (i.e., trypsin). It is also desirable and preferable to find compounds with advantageous and improved characteristics in one or more of the following categories, but are not limited to: (a) pharmaceutical properties (e.g., solubility, permeability, and amenability to sustained release formulations); (b) dosage requirements (e.g., lower dosages and/or once-daily dosing); (c) factors which decrease blood concentration peak to-trough characteristics (e.g., clearance and/or volume of distribution); (d) factors that increase the concentration of active drug at the receptor (e.g., protein binding, volume of distribution); (e) factors that decrease the liability for clinical drug-drug interactions (e.g., cytochrome P450 enzyme inhibition or induction); (f) factors that decrease the potential for adverse side-effects (e.g., pharmacological selectivity beyond serine proteases, potential chemical or metabolic reactivity, and limited CNS penetration); and, (g) factors that improve manufacturing costs or feasibility (e.g., difficulty of synthesis, number of chiral centers,*

chemical stability, and ease of handling).'"

938. Counsel then asked Prof. Taft to summarise what, in his view, that passage is teaching? To this, Prof. Taft responded as follows:

> "[T]*he beginning of the passage discusses looking for specific inhibitors of factor Xa with improved characteristics, such as improved activity and selectivity. But then it goes on to list, in that paragraph, (a) through (g), were a bunch of preferable characteristics. And a person of ordinary skill looking at that paragraph would immediately recognise that those characteristics or objectives are focusing on pharmacokinetics and in consideration of factor Xa inhibitors and where they work in the body, which is specifically in the bloodstream, that a person of ordinary skill in pharmacokinetics reading those objectives would see that it points to a specific desired pharmacokinetic profile for a factor Xa inhibitor that was being looked at to be developed into a medicine. And I've outlined that in my statement. And in my opinion...what a person of ordinary skill would see is that would be a medication that would have what we call a small volume of distribution – that would be a drug that resides primarily in the bloodstream after it's dosed. And that would also need to have what we call a very small clearance – and that's the way that the drug is metabolised and excreted by the body. Because in order to have those two attributes, what you wind up with is a drug that you could give potentially for once a day dosing and it would have reduced fluctuation between the highest and lowest plasma concentrations seen after the dose. And that's consistent with a drug with a relatively long half-life. And so, in the eyes of a skilled pharmacokineticist, that is the ideal profile that's expressed in that that italicised passage from the 652 application.*"

2. Synthesis

939. Counsel for BMS asked Prof. Taft to summarise his views in relation to the skilled pharmacokineticist seeing the quantity of Example 18 that was synthesised and what conclusions he would draw from that. To this, Prof. Taft responded as follows:

> "[A] *person of ordinary skill would recognise that Example 18 is the only compound in the 652 application that was scaled up into gramme quantities of material. And a skilled pharmacokineticist knows that if you see a compound that shows promise during the initial screening, to move it forward into advanced pre-clinical testing requires gramme quantities of material to run the types of experiments that would need to be done, including the key experiments to evaluate in detail the pharmacokinetic profile. So, in my opinion, a person of ordinary skill would look at Example 18 to signify that the inventors were focussed on that particular compound, given it's the only one that was scaled up into those gramme quantities.*"

940. In response to a further query from counsel, Prof. Taft confirmed that he continued to hold those views regarding the amount of Example 18 that was made which he sets out at §§89–93 of his first witness statement.

D. Cross-Examination

1. No Need for Prof Taft's Evidence?

941. Counsel for Teva noted that Prof. Taft had previously given evidence in various other jurisdictions – Prof. Taft indicated that he had done so in Canada, Finland, Sweden , and the United Kingdom – and put it to him that he would therefore be aware that (i) it is the position of Teva that pharmacokinetic evidence is not relevant to the present proceedings (Prof. Taft acknowledged a general awareness of this fact) and (ii) the position being taken by Teva throughout is that patent

application 652 does not have practical interest to a pharmacokineticist (again Prof Taft confirmed that this was so).

942. Counsel for Teva also brought Prof. Taft to a ruling by Meade J. in the parallel English proceedings to the within proceedings. That ruling followed an application made in England against BMS (who also instructed Prof. Taft there) for indemnity costs to be awarded against them because of the fact that they called his evidence, despite the view of Teva that it was not relevant evidence in terms of the interpretation of the patent application. In the course of his ruling, Meade J. expressed his view that "[t]*he...need for DMPK expert evidence was always objectively very thin*" and proceeded to order indemnity costs against BMS for having adduced Prof. Taft's evidence.

943. Counsel for Teva explained that in making the foregoing points she "*just wanted to make you* [Prof. Taft] *aware of that state of play and to make you firmly aware that Teva's view is that your evidence is not of relevance to these proceedings and is not evidence that assists the Court in interpreting the issues in relation to Patent Application 652.*" So although she proceeded to test Prof. Taft's evidence she did so "*purely and strictly on that basis.*"

944. Counsel for Teva also adverted to the fact that the agreed CGK section on pharmacokinetics is expressly stated to be without prejudice to Teva's position that WO652 is not addressed to the skilled DMPK scientist. Asked if he recalled that this was the position of Teva in the English proceedings, Prof. Taft indicated that he did not recall reading this in the agreed CGK document but was satisfied that if that is what it says (it is) then that is what it says. Subject to the foregoing being the position of Teva, counsel for Teva asked Prof. Taft to confirm (and he duly confirmed) that the material in the agreed CGK document is largely derived from his evidence and that of Dr Reed, who also gave evidence in the English proceedings.

945. I have already indicated in Part B above how I have treated with Prof. Taft's evidence in these proceedings.

2. Professor Taft's Evidence in Canada

946. Through a series of questions counsel for Teva elicited the following facts from Prof. Taft: (i) he was provided with three documents for the purpose of preparing his witness statement, viz. the patent, the 652 application, and the 131 patent application; (ii) he stood over his assertion at p.6 of his statement that where he had included information therein that did not come from his own personal knowledge he had stated the source and in each case believed the information to be true; (iii) that he was a witness in Canada and gave oral evidence and was cross-examined in Canada; (iv) the Canadian proceedings were based on an assessment of the patent with the claim as to apixaban in the patent; and (v) as a consequence, when Prof. Taft gave his evidence in Canada, it was based on knowing that apixaban was the sole claimed compound.

947. Counsel for Teva then turned to the substance of Prof. Taft's witness statement in the Canadian proceedings, in particular where he states that "*The skilled pharmacokineticist would also understand from the 202 Patent that the inventors achieved this research objective with at least one compound – apixaban*" and then proceeds to state:

> "*a.* *The 202 Patent presents a genus of lactam-containing factor Xa inhibitors and more than a hundred different examples of making many of those compounds.*
> *b.* *However, it is telling that from this genus only one compound is claimed in the 202 Patent.*
> *c.* *From this, the skilled pharmacokineticist would have reasoned that the inventors must have discovered that apixaban was an exceptional factor Xa inhibitor that met their research objectives*",

Counsel for Teva also noted Prof. Taft's later averment in that statement that his opinion was

reinforced by the fact that not only is apixaban the only compound of the exemplified compounds to be claimed, it was the only exemplified compound to be made in multi-gram quantities.

948. Counsel for Teva then brought Prof. Taft to a further passage in his witness statement in the Canadian proceedings where he observes as follows:

> "*The 202 Patent contains hundreds of pages and presents a genus of lactam-containing factor Xa inhibitors. While the synthesis for a number of compounds are provided in the patent's examples, no data specific to any compound is provided. When it comes to apixaban, however, none are needed. The skilled pharmacokineticist would have found it remarkable that only apixaban features in the claims of the 202 Patent. The skilled pharmacokineticist would have reasoned that the inventors must have determined that apixaban was an exceptional factor Xa inhibitor*",

noting that Prof. Taft then immediately refers to the fact that he had also recognised that the patent provides the synthesis and crystallisations for apixaban in Example 18.

949. Counsel for Teva then put it to Prof, Taft (and he agreed) that on the basis of his report as presented to the Canadian court, the first reason he gave for his opinion about apixaban was based on the fact that it was the one that was claimed. At this juncture the following exchange occurred between counsel for Teva and Prof. Taft concerning his evidence in Canada:

Counsel:	[T]*he exercise in Canada was based on knowing that apixaban was the claimed compound....*[a]*nd you formed your view about its exceptional features based on knowing it was apixaban and that was your basis for your opinion as to the compound in the patent in Canada..?*
Prof. Taft:	*....I think if you read my entire report...you'll see how my opinions were formed and framed. I acknowledged that in that particular case it was the patent itself and the claims were part of the exercise that I evaluated.*

...

[Counsel for Teva then quoted certain portions of Prof. Taft's evidence in Canada:]

Counsel: ...You're asked about your understanding about the invention:

> '*Your understanding is that the invention of the 202 Patent is that apixaban had 18 special pharmacokinetic properties, is that right?*'

....You answer:

> '*No, that's not my understanding of the invention. What I'm trying to provide is what I was asked to do in this case and opinions that I arrived at. My opinions are related to the pharmacokinetics, the pharmacokinetic properties and the significance of apixaban being the only element claimed, I guess it's in claims 1 and 2."*

Then you continue:

> *'As far as the other claims and other elements of the invention, I wasn't asked to opine on those things and I would certainly look towards other members of the skilled team.... which may be a medicinal chemist or a clinician. And so I don't want to, I want to make sure that I'm clear my opinions are related specifically to how a skilled pharmacokineticist would view the 202 Patent and the claim of only apixaban in claim 2.*'

950. Asked:

(i) if the foregoing summarised his evidence or represented certainly an element of his evidence to the Canadian court, Prof. Taft responded that it represented an answer to one of the questions that he was asked during cross-examination,

(ii) to confirm that he was not saying that the fact that apixaban was claimed as the compound in the patent that he was looking at in Canada, *i.e.* not a key part of his assessment in Canada, Prof. Taft responded that he was not saying this, that he was merely trying to answer the questions being asked and make sure that it was a proper characterisation of his testimony,

(iii) if the fact that apixaban was claimed as the compound in patent 202 in Canada was an important part of his analysis and evidence in Canada, Prof. Taft indicated that it certainly supported his conclusions and his opinions,

(iv) when he set out his opinions, was it not the first matter that he relied upon to substantiate his views about the patent, Prof. Taft responded that he did not recall his thought process or the ordering of same.

951. As regards the ordering of Prof. Taft's thought process, counsel for Teva brought Prof. Taft to para.25 of his Canadian witness statement, at which juncture the following exchange occurred:

Counsel: ...[In] paragraph 25....[y]ou say [that].... '*The skilled pharmacokineticist would also understand from the 202 Patent that the inventors achieved this research objective with at least one compound – apixaban.*' You list three reasons, (a), (b) and (c). And the second one is: '*It is telling that from this genus only one compound is claimed....c. From this...*' – so, I'm reading that as being the sequential statement from the previous one – '*c. From this, the skilled pharmacokineticist would have reasoned that the inventors must have discovered that apixaban was an exceptional factor Xa inhibitor that met their research objectives.*' You then say: '*This is reinforced by the fact that not only is apixaban the only compound of the exemplified compounds to be claimed... it was the only* [compound] *exemplified... in multi-gram quantities.' But if you read sub-paragraph (c), I would put to you that that clearly says that you were talking about the fact apixaban was the only compound claimed as being the basis on which you reached the statement you made in sub-paragraph (c). Are you disputing that?*

Prof. Taft: *...I'm not necessarily disputing it, I'm just trying to answer your questions as best as I can. I acknowledge that in the Canada proceedings it was the patent itself and the claims were part of the patent....*

Counsel: ...[B]*ut a very important part of that opinion was the fact that*

apixaban was the claimed compound in the Canadian proceedings..?

Prof. Taft: *...I'm not a legal expert and I don't know what the differences are between Ireland and Canada. But that was the part of the Canadian proceedings, was the patent itself. And the claims were part of that, yes....*

Counsel: *But in paragraph 25, I do have to press you on this, Dr Taft, because what you say there is that it's telling that the only compound claimed is apixaban. And you say from this you would've reasoned the inventors must have discovered that apixaban was an exceptional inhibitor. So, you are linking the fact that apixaban was identified with your conclusion; do you accept that?*

Prof. Taft: ...[A]*s it's written in paragraph 25, that's what it says.*

Counsel: *Yes, thank you. You don't refer anywhere in your witness statements in this jurisdiction to your report in Canada. You mention you gave evidence in Canada. You don't mention that you knew what apixaban was. You don't mention that the Canadian proceedings were concerned with a patent for apixaban was identified. You don't make any reference to your acknowledgement that you had hindsight in coming to give evidence in these proceedings. Can you explain that?*

Prof. Taft: *...I believe it was the second case that I was involved with...in England...that that was made clear to me that...my objective was to view it from a person of ordinary skill, based on the application. And that's what I arrived at in setting forth my opinions. I ignored, for the purposes of the England trial, the fact that there was a patent and the patent claims. I focused on the application to arrive at my opinions.*

Counsel: ...[Y]*our witness statement here is not the same as the witness statement in the UK....In your witness statement for these proceedings, did you put anything in there that acknowledged your knowledge of apixaban?*

Prof. Taft: *...I acknowledged that I was involved in these cases beforehand. As far as my knowledge of apixaban, when I set forward in my Canadian report, I did not know very much about apixaban. And so I guess it's fair, if I was supposed to put in statements about my knowledge of apixaban from my previous cases...it's not there in detail in this statement.*

Counsel: *...Paragraph 5.3 of your statement in the UK proceedings reads as follows:*

> *'In my expert reports in the Canadian proceedings, I note that apixaban is the only compound from the CA 202 genus of lactam-containing compounds featured in its claims. I have been informed that the fact that the Patent only claims apixaban in its granted form is not something that I should have regard to for the purposes of the UK Proceedings.'*

You see that paragraph..?

Prof Taft: *Yes....*

Counsel: *Is there a similar statement anywhere in your witness statements for these proceedings?*

Prof. Taft: ...[N]*o....*
Counsel: *I'm not going to get into explaining it to you, Dr Taft, but it's very important that the patent is not the basis for your expert opinion in these proceedings and shouldn't have been the basis for your opinion in these proceedings.*
Prof. Taft: *Yes, and it wasn't.*
Counsel: *But you don't address that in your witness statement or how...knowing apixaban wasn't the basis from which you approached your task. There's no statement equivalent to paragraph 5.3 in the English statement.*
Prof. Taft: *I think I've already answered that.*

952. I have already indicated in Part B above how I have treated with Prof. Taft's evidence in these proceedings.

3. Professor Taft's Experience

953. Asked whether:

(i) although he is an expert pharmacokineticist, he has primarily, if not exclusively worked in an academic position, Prof. Taft confirmed that his full-time position for almost 30 years has been at Long Island University as a member of the faculty there,
(ii) he has been involved in early drug development of any drugs, Prof. Taft indicated that he had been,
(iii) any of that work concerned anticoagulants or antithrombotics, "*looking, obviously, pre-2001, which is the priority date*", Prof. Taft indicated that the compounds on which he had worked were not anticoagulants,
(iv) he has any experience of working with factor Xa in his career, Prof Taft indicated that he had not,
(v) he has any experience or qualifications in medicinal chemistry, Prof Taft indicated that he had not.

4. Literature Search

954. Turning next to the doing of a literature search, counsel for Teva noted that Prof. Taft, in his witness statement, had asserted that if a pharmacokineticist is assigned to a new project, what she would typically do is undertake a literature search to educate herself about the target enzyme. Prof. Taft confirmed that this was so, that "*In any therapeutic area, you'd want a general understanding of the current knowledge about that treatment or particular disease.*" At this juncture the following exchange occurred between counsel for Teva and Prof. Taft:

Counsel: ...[H]*ow would you gain that understanding? ....*
Prof Taft: *Well, you're working with members of a team, so you could certainly go to the literature and do that on your own, or perhaps consult with a clinician or a pharmacologist and give you some background.*
Counsel: ...[I]*n this case, what did you do..?*
Prof. Taft: ...[F]*or these proceedings, it would be similar; I had a general understanding of factor Xa. A person of ordinary skill may not have had the same experiences that I did. So, to go and look at a general overview of where factor Xa fits within the coagulation cascade. And then doing, as I laid out in my statement, what was known in the field about the search for or the development of factor Xa compounds....*

Counsel: *Where in your statement do you explain how you identified relevant sources that an ordinary skilled pharmacokineticist would've done?*

Prof. Taft: *...I don't know if I listed where I would find those sources. But you could find them through a literature [search]. And a person of ordinary skill knows how to do that. Or a member of the team may provide references relevant to his or her field and share that with other members of the team....*

Counsel: *Did you carry out searches?*

Prof. Taft: ...[S]*ome of the articles that I cite, my recollection was that I found those.*

Counsel: ...[W]*here do you explain in your witness statement the searches you undertook to find those?*

Prof. Taft: *I don't know if I provided that level of detail in my witness statement.*

Counsel: *I think your witness statement in fact only states...that you were given the patent, the application for the patent and 131. You don't identify...any of the other sources used in your witness statement....Can you explain that?*

Prof. Taft: ...[M]*ost of what you're showing on the screen, any references...there are...mine....*

Counsel: *But you didn't work previously in factor Xa. So, how did you have them? ...*

Prof Taft: *I think a person of ordinary skill could do a search and find the articles that I referenced about factor Xa. That's how I found them.*

...

[Counsel for Teva then brought up some of the titles of journals and articles referred to in Prof. Taft's witness statement, with a view to his confirming that they were ones that he had identified and would typically read from his interest in pharmacokinetics].

Counsel: ...[I]*s it your evidence that you identified each of these articles yourself?*

Prof: Taft: *I can't say I identified each of these articles myself, no.*

Counsel: ....[D]*id you, in your witness statement, disclose the fact that you didn't identify all the sources in it yourself?*

Prof. Taft: *No....*

Counsel: *You understand that it's important, as an expert witness, that you disclose to the court the sources you're relying upon and how you identified them, so that the court can be satisfied as to how it marries with what an ordinary skilled pharmacokineticist would have done at the priority date?*

Prof. Taft: *I don't recall being made aware of that....*

Counsel: ...[W]*ould it surprise you to know that seven of the articles you cite were also the same ones that Dr Young relied upon for the purpose of his witness statement in these proceedings? ...*

Prof. Taft: *...I did an extensive search, looking for information on the pharmacokinetics of compounds under development before 2001 and I'm not surprised if there were similar articles there that that people would've pulled. This was the state of the art in the field at the time of the invention....*

Counsel: ...[Y]*ou're standing by your evidence that you identified these articles as being relevant? ...*

Prof. Taft: *I don't remember which ones I was given and which...I found myself. But I do know that I did my own search and found my own articles that were relevant that I've cited in this report.*

5. The 652 Application

a. Various

955. Asked whether:

(i) he has said repeatedly in his evidence in various jurisdictions that there is no pharmacokinetic data in the 652 application, Prof. Taft confirmed that this was so,

(ii) he had said in Canada that "*there's* [no] *solubility tests or data...no permeability tests...no references to half life...no information about sustained release dosage...no results for protein binding...no data on drug on drug interactions*", Prof. Taft indicated that this was a fair statement of what he had said,

(iii) he had said in the UK that "*there's no data available or provided in the application*", Prof. Taft agreed,

(iv) he had said in his witness statement for the present proceedings that most of the patent application is of more interest to a medicinal chemist than to a pharmacokineticist, Prof. Taft confirmed that this was so,[6]

(v) as a pharmacokineticist, Prof. Taft would typically read the synthesis sections where it describes how compounds are made, Prof. Taft indicated that typically he would not,

(vi) he had said in the UK that it would be a challenge for him to draw out structures from chemical names, Prof. Taft indicated that this was so (it seems because of his not being a medicinal chemist),

(vii) he does not know much about synthesis, because he is not a medicinal chemist, Prof. Taft indicated that "*I leave that area up to the people that are experts in that field. I stay in my lane. Organic chemistry is not my strong suit*",

(viii) he has previously accepted in Canada (and as is also stated in the agreed CGK document) that it is common general knowledge that if a drug is operating in plasma that it would be desirable that it would have a low volume of distribution, a low clearance and a decent half life, Prof. Taft indicated that this was so,

(ix) the just-mentioned view is based on CGK, Prof. Taft eventually agreed,

(x) it was his view, as stated in para.93 of his first witness statement, that

> "*The skilled pharmacokineticist would have understood from the research objectives set out on page 6 of the Application that the inventors had advanced drug discovery goals in mind in their search to find a novel anticoagulant that was capable of being*

[6] Counsel for Teva observed at this point, "*And in fact I think almost every witness agrees with that; certainly every witness on behalf of Teva has agreed that the application is directed to a medicinal chemist and of interest primarily to a medicinal chemist.*" Shortly after, the following exchange occurred between counsel and myself:

Judge:	*Is that right, what you just said? Dr* [Wargin]*...didn't he say...he thought it would be both a medicinal chemist and a pharmacologist? ...*
Counsel:	*He said it would be of interest to both. But my recollection...was that a lot of the synthesis sections and a lot of it would be more of interest to a medicinal chemist....*
Judge:	*Right. I did ask him that, though. And I think he said 'Yeah, I think both'....*
Counsel:	*But certainly there hasn't been a dispute that it is primarily directed to medicinal chemists....*
Judge:	*Well, that's the question I'm asking. I think Dr Wargin said both.*
Counsel:	*Both a pharmacologist and a – yes, but not a pharmacokineticist, I suppose.*
Judge:	...[N]*ot a pharmacokineticist, exactly.*

studied in the clinic and used as a drug,"

Prof. Taft confirmed that p.6 is referring to advanced research objectives and that "[T]*he skilled pharmacokineticist would be able to understand from those research objectives what the ideal profile would be*",

(xi) whether it was his view (by reference to para.94 of his witness statement) that the content of page 6 teaches specifically what the inventors were trying to achieve, the following exchange occurred between Prof. Taft and counsel for Teva:

Prof. Taft:	*What it shows is that the ideal profile for a drug that works in the bloodstream would have those characteristics, yes....*
Counsel:	*The desired profile of any drug that works in the bloodstream..?*
Prof. Taft:	*That would be the desired profile if you had these goals of increasing the concentration of drug at the receptor, allowing for the potential for reduced doses or once-daily dosing. And for a drug trying to reduce the fluctuation that happens with the plasma profile within a dosing interval, this would be the ideal from a pharmacokinetic perspective, the ideal compound that you would be looking for to develop into, potentially into a druggable, a drug to treat a condition.*
Counsel:	*Just looking at what's on page 6, it talks about what's desirable and preferable and it talks about 'improved characteristics in one or more of the following categories but are not limited to.' ....And I think paragraphs (a) to (g), I have to put to you, Dr Taft, are simply generic headings that are a wish list for any drug. And that is the evidence that has been given by several witnesses in the various jurisdictions in these proceedings....*
Prof. Taft:	*...I don't disagree that these are general categories that potentially apply to any drug development project. But when you're looking at, specifically, a medication or a target that's within the bloodstream, there is an ideal pharmacokinetic profile that exists. And that is not common....among medications. Most medications don't have that profile. But that is the ideal profile for a drug that works in the bloodstream.*
Counsel:	*Dr Taft, the question I'm asking you concerns page 6, not what a skilled pharmacokineticist would know from*

	their pre-existing common general knowledge. I'm looking for you to identify where, on this page, there is information that you're interpreting, using your common general knowledge? ...
Prof Taft:	*...I'm confused by your question....I acknowledge that any...drug development project would be looking for some of these characteristics....But you drill down into the actual development project that you're looking at here, which is a drug that works in the bloodstream, and it makes an ideal desired profile....*
Counsel:	*....What I'm asking you to do is to look at page 6 and unless you can identify something in page 6 that is teaching you a profile, I'm putting it to you that the only source you're using for what you're saying an ideal pharmacokinetic profile is CGK? ....I just have to put to you one final time that page 6 doesn't set out any specifics regarding any parameters or targets or goals, it just sets out a....generic wish list, which I think you've agreed with, Dr. Taft, so I'll move on.*

b. Synthesis

956. Counsel noted that Prof. Taft had also focused on the synthesisation of how patent compounds were made, with Example 18 being the one that he identifies and emphasises in his witness statement. Counsel then turned to ask him certain questions in this regard.

957. Counsel noted that at para.90 of his first witness statement, Prof. Taft states as follows:

> "*Example 18 does not expressly state that the scale up was conducted in order to prepare material to permit preclinical testing in animals to establish apixaban's pharmacokinetic profile. However, the skilled pharmacokineticist would have known that lead compounds are subjected to extensive testing.*"

958. Asked why he used the words "*does not expressly state*", Prof Taft indicated that this was because Example 18 'does not expressly state' (what he states it not expressly to state).

959. Asked if it was stated by implication, Prof. Taft indicated that:

> "[T]*he skilled pharmacokineticist would have known that these compounds are subject to extensive testing, [and] that...in the eyes of a skilled pharmacokineticist, the fact that Example 18 is the only compound that's scaled up to gram quantities would signify that that's a compound that the inventors are focusing on in bringing it forward to more advanced testing*".

960. Asked why he used the words "*lead compound*", *i.e.* a 'leading compound', not a compound containing the metal lead, the following exchange occurred between Prof. Taft and counsel for

Teva:

Prof. Taft: ...[G]*enerally, in the discovery stage you may be screening a number of different compounds requiring very small quantities of drug or compound. But when you identify compounds that look like they have the potential, you want to bring them forward to more advanced testing, as I outlined in my statement. And if I used the word 'lead compounds', that would be compounds emerging from your discovery programme that you want to test further to –*

Counsel: ...[W]*hy are you using the words 'lead compound' to interpret Example 18?*

Prof. Taft: *Well, in the eyes of a skilled pharmacokineticist, the fact that that's the only compound that's been skilled up to gram quantities would signify that the inventors are particularly focused on that....*[and] *interested in and bringing forward to more advance preclinical testing....*

Counsel: ...[Y]*ou say in the final line of paragraph 92...*[that] '*It suggests that apixaban's initial pharmacokinetic results were quite promising and larger-scale studies were required*'....[a]*nd you continue in paragraph 93 to conclude that... 'The skilled pharmacokineticist would have concluded that apixaban had been scaled up for in depth evaluation'. So, they're conclusions you reach arising from your identification of apixaban in Example 18..?*

Prof. Taft: ...[I]*t's based upon Example 18 being the only example that was scaled up to gram quantities and what, in my opinion, how a skilled pharmacokineticist would interpret that.*

Counsel: *So, your evidence is that you, as a skilled pharmacokineticist, would've picked up the patent application and identified this fact and would've drawn the conclusion that apixaban was remarkable and that this was so significant that it indicated that apixaban must have been scaled up for further testing, is that your evidence?*

Prof. Taft: *...I believe my evidence is that* [to] *a person of ordinary skill in pharmacokinetics, that information about the scale-up in Example 18 would've been identified by a medicinal chemist as a member of the team. But being made aware of that and a recognition that's the only compound scaled up to gram quantities, that supports my opinions of how a pharmacokineticist would interpret that*.

961. Counsel noted at this juncture that she did not recall any mention in Prof. Taft's witness statement "*about having been told this by a medicinal chemist or another member of the team*". When her attention was drawn to the last sentence in §86, which states that "*This is the type of information that the medicinal chemist would have told the pharmacokineticist*", counsel contrasted what is said there with what Prof. Taft indicated in his witness statement in the UK proceedings, which was that he was told by Dr Camp (whom I understand to be the medicinal chemist who gave evidence in England and Wales). At this juncture, the following exchange occurred between Prof. Taft and counsel for Teva:

Prof. Taft: *...I see that that was information that was provided to me by Dr Camp. And what I say...in this case is I refer to this type of information that the medicinal chemist would have told the pharmacokineticist.*

Counsel: *....I have to put to you that you've put evidence forward in your witness statement to this court as if it was the evidence of a skilled pharmacokineticist when in fact it's clear it's based on the*

evidence of a medicinal chemist who gave evidence in England..?

Prof. Taft: *....I stand by paragraph 87 in terms of synthesising gram quantities of highly pure apixaban.*

[Paragraph 87 states as follows:

> "*The skilled pharmacokineticist would also have considered it significant that Example 18 is the only example in the Application to have two crystallization purification steps. The inventors initially obtained 2.5 grams of apixaban (which is already a large amount in this context), and then conducted a recrystallization to obtain another 0.57 grams of apixaban, for a total yield of 3.07 grams. This would have told the skilled pharmacokineticist that the inventors were trying to synthesize large quantities of highly pure apixaban for advanced testing*."]

That's what you would need; gram quantities of a pure compound....You always want to conduct testing with highly pure compound and you need material to do it.

962. Asked whether:

(i) as a skilled pharmacokineticist reading a patent application, he would have considered it important if two or one crystallisation purification steps were carried out, Prof. Taft indicated that he did not know,

(ii) he himself noticed the amount that was synthesised in Example 18, Dr Taft's recollection was that "*That was probably pointed out to me by perhaps I think an attorney*",

(iii) in terms of the conclusions he seeks to draw from the fact that 3g was made of the compound in Example 18, was he aware that there were other compounds synthesised in the patent application where the reader is not told how much was made, Prof. Taft indicated "*I think that's fair. Perhaps some of the examples don't indicate the quantity, yes, I believe that's correct*",

(iv) he was aware that there were other matters that could be told to him about a compound that had been made such as, *e.g.*, purity data about a compound, or mass spectrometry data and whether that was something he would have considered, Prof. Taft responded "*I don't know. If it's not within my area of expertise I'm not sure I would have considered it....Perhaps there's someone else with that expertise that would answer that question*",

(v) by reference to the last-mentioned answer it was the case that in truth the only person who could really give any opinion about the relevance of the synthesis section of the patent was a medicinal chemist, Prof. Taft disagreed, observing that "[I]*t's significant that that is the only compound that was synthesised to that quantity and that means something to a skilled pharmacokineticist who would be conducting the advanced clinical testing to look at pharmacokinetic properties*",

(vi) given that he is not a medicinal chemist he is in a position to compare the synthesis steps that are undertaken in the different examples in the patent application, Prof. Taft indicated that he was not,

(vii) there can be other reasons for making more of one compound or another, that he is not aware of as a skilled pharmacokineticist, Prof. Taft indicated that this was so,

(viii) given that he is not a medicinal chemist, he could dispute the evidence given

by Dr Camp in England where Dr Camp stated in evidence that there may be other reasons why the amount was larger, such as that the chemistry just worked better, Prof Taft responded "*Yeah, I don't dispute that at all*",

(ix) he could opine on there being different reasons for the amount that was made of one compound, such as Example 18, even if it was the largest amount, Prof. Taft indicated that he "*wouldn't be asked to opine on that. That's something a medicinal chemist should answer*".

963. Turning to what Prof. Taft could opine upon, and, in particular, to §89 of his first witness statement, where he outlines the amount of material needed for *in vivo* experiments, and mentions that "*An experiment of this type would require significantly more material (50mg in this example)*", counsel had Prof. Taft agree that he was talking there about *in vivo* testing in dogs. At this juncture the following exchange took place between counsel for Teva and Prof. Taft:

Counsel:	*So, your evidence is that you could undertake an in vivo test in a dog with 50mg of product..?*
Prof. Taft:	*Based on what's the typical dose you would use in a dog study, that would be how much material would it take to dose one dog.*
Counsel:	*....And I think it's in the agreed CGK document and...based on your own evidence, from which that derives...*[that] *how much drug you need to do a test, or how much compound you need to do a test will depend on the goal of the experiment, the species of the animal and...on the potency of the compound, for example. So, it's difficult to have an abstract idea of how much compound you need to do an in vivo test..?*
Prof. Taft:	...[F]*or a pharmacokinetic study...potency doesn't come into play.*
Counsel:	*....But the species of the animal, the goal of the experiment, and so forth, they're things that you have to factor in when...deciding how much you need to do a test..?*
Prof. Taft:	...[E]*arly screening experiments...would be in a mouse or a rat and those are relatively small animals so the amount of material you need is really small. But when you move into advance testing you're going into big animals, dogs, primates. The amount of material you need is higher because you dose them on a milligram per kilogram basis and they're just bigger animals.*
Counsel:	*But your evidence is that 50mg is enough dose for a dog in vivo testing..?*
Prof. Taft:	*And a dose of about 5 to 10mg per kilogramme...based on the reference of a Beagle dog.*
Counsel:	*....So, when it comes to the evidence you've given about Example 18 and the conclusions you draw from it, am I correct in understanding that what you're effectively saying is that if you were told there was 3g of a product available for testing, you could give an opinion as to what testing could be done with that amount of product? ...*
Prof. Taft:	*I don't understand the question....*
Counsel	...[Y]*ou're not giving an opinion as to anything regarding why that amount may have been made, or what other uses it may have been put..?*
Prof. Taft:	*...I'm basing it on how a person of ordinary skill in pharmacokinetics could look at that quantity as related to the other quantities...for the other examples in the patent....*
Counsel:	*....So, you could be told that there's 1g of one product and you could say what you could do in terms of testing it, but I suppose it would be pure speculation...for you to try and say, from this patent*

application, how much of any compound is available for testing?

Prof. Taft: *Well, what I've seen is that Example 18 is the one compound that was scaled up to gram quantities. As...*[for] *your question...you have to base it on what's in the patent or the application....*

Counsel: [Having noted the evidence of Dr Hermkens in the Dutch limb of these proceedings that '*Example 99 uses 1g of the final product of Example 19 (i.e. one third of the amount produced in Example 18)',* counsel put it to Prof Taft that*:*] [I]*t could easily be that that is 1g of the 3.07g in Example 18. Do you have any comment to make on that?*

Prof. Taft: *...I've acknowledged that there may be other reasons for scaling up to gram quantities but I stand by my opinions in my statement; ...I presume...*[Dr Hermkens] *is a medicinal chemist...and so, those questions would be better posed to a medicinal chemist than to me.*

Counsel: *....So, as a pharmacokineticist you simply can't say what the relevance of the amount synthesised in Example 18 is*[?]....

Prof. Taft: ...[A]*gain, I'm basing my opinions on how a skilled pharmacokineticist would view the patent application and that's how I based my opinions about the scaled up gram quantities....*

Counsel: *I have to put it to you that the only basis you've said in evidence or stated in your witness statement to justify any conclusions in Example 18 is that you were told by Dr. Camp that there was a particular synthesis undertaken and that this disclosed that Example 18 was one of significance?*

Prof. Taft: ...[N]*o...the knowledge that that is the only example scaled up to gram quantities...that's what I based my opinions on.*

964. For what it is worth counsel brought Prof. Taft next to a patent that had been filed by BMS on 16th September 2002 (a patent to do with the treatment of pathological conditions such as rheumatoid and osteoarthritis; corneal epidermal or gastric ulceration and other such conditions) and had him confirm on the spot that the language used in part of that patent application was akin to that used in the 652 application. I expressed doubt on the day, and express it again here, as to whether anybody is capable of undertaking such analysis in the witness box. Certainly I attach little to no weight to an answer given in such circumstances. Prof. Taft's answer was that it appeared to him that the language deployed in each document was the same.

6. Lack of Credibility

965. By way of closing remark, counsel for Teva posited that the credibility of Prof. Taft's evidence in relation to p.6 of the 652 application "*is just not substantiated*". To this, Prof. Taft responded that "*I stand by the statement in my report and how a person of ordinary skill would read page 6 in terms of an ideal pharmacokinetic profile for a factor Xa inhibitor.*"

E. Re-Examination

966. There was no re-examination of Prof. Taft.

XI. THE MEDICINAL CHEMISTRY EVIDENCE

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The Evidence of Dr Edwards

A. Introduction

967. Dr Edwards is an experienced medicinal chemist with over 25 years of experience working in drug discovery within the pharmaceutical and biotechnology industries. In his first witness statement, Dr Edwards states, amongst other matters, as follows:

> "*I was asked by Pinsent Masons (Ireland) to act as an expert witness in the*[se] *proceedings....I understand that Teva has brought an action against BMS Holdings Ireland Unlimited Company...to revoke BMS' European Patent IE No 1 427 415....I was asked to consider what a medicinal chemist working as part of a team, interested in developing a factor Xa inhibitor, would have known about factor Xa inhibitors, as of 21 September 2001...which I was told was the key date for the proceedings and which I also now know is the priority date of the Patent*",

and (at §§1.2-1.3) of his second statement :

> "*I have been provided with Dr Young's report, along with the documents he provided and those with which he had been provided. I have been asked to respond to Dr Young's report.*"

968. Subject to para.4 of this judgment, an abridged version of Dr. Edward's written evidence is set out at Appendix 3. I respectfully invite readers of this judgment to read that appendix and then resume reading here. An account of the evidence that Dr Edwards gave when examined, cross-examined, and re-examined follows hereafter.

A. Examination

1. Skilled Person

969. Counsel for Teva indicated her understanding that the concept of a skilled person had been explained to Dr Edwards, being a person who has a practical interest in the subject matter of a patent and who would be uninventive but have a common general knowledge in the field. She noted that prior to preparing his witness statements Dr Edwards had been provided with WO 131 and WO 652 and asked him, following on his review of those documents, who he thought the skilled person would be for the purposes of 652. To this, Dr Edwards answered as follows:

> "*I believe both are mainly directed at medicinal chemists. There's obviously some synthesis information in there, so synthetic skills would be important. But at that stage in 2001, usually the medicinal chemists would also have a synthetic chemistry background, so it could be one in the same person. So, for me, predominantly it's chemistry.*"

970. Asked whether there were any other persons with whom he thought a medicinal chemist would work with if they were involved in practical application of the invention in the patent application, Dr Edwards responded that "*a pharmacologist would be someone, I think, that a medicinal chemist would work with.*"

2. Literature Search

971. Counsel for Teva noted that Dr Edwards, in his witness statement, describes the literature

search that he has conducted. She asked him to explain the parameters of that search and how he identified the documents that he listed in his report. Dr Edwards responded as follows:

> "*I would've looked for general terms to start with, which would've provided a larger number of returned hits. So, Factor Xa, for example, was the initial search. That produced several thousand returned hits, which were too many to really work through practically. So, I changed that to Factor Xa inhibitor, and that returned a much smaller number of hit documents that I looked through. So, I took the view* [that] *at this stage in 2001...the field was active but still very early. Most of the companies were looking for inhibitors with sufficient properties to validate Factor Xa as a target rather than - and of course, it still was a goal - but rather than, at that stage, having particular clinical trials and advanced clinical trials of compounds in development, it was more 'Let's validate the targets'.*
>
> *So... I took the view that obviously literature references directly relevant to Factor Xa would be important, but also looking at similar serine proteases - thrombin, for example, TPA - was there any direct information in related targets that measured properties of Factor Xa? That could give an indication of SAR against a related target that may be imported into Factor Xa research. So, I took the view that I wanted to encompass related targets as well as focus just on -- not focusing just on Factor Xa.*"

972. Asked later by counsel for Teva whether the above literature search was similar to what he would typically do if he came to a new drug development programme, Dr Edwards responded as follows:

> "*Yes, for a project at this stage which is, as I say, relatively early and still looking for proof of concept for Factor Xa inhibitors and the target, I would certainly do this exact literature search that I did do.*"

3. Enzyme Experience

973. Asked, as an experienced medicinal chemist, the experience that he would expect to have in a given enzyme target before he would join (or upon joining) a drug development team, Dr Edwards responded as follows:

> "[M]*edicinal chemists are quite routinely used in many different areas of drug discovery in terms of synthesis and design. So, they're not necessarily someone who would have...direct experience, of enzymes, it could be someone who's worked on a completely different target – they may have worked in inhalation or topical delivery rather than oral. But the skill set is broad enough that you adapt very quickly, you take in learning from the team and from outside. So, it is possible that you would have experience of enzymes, working on enzyme-based targets, but also it could be the case that you don't have that direct experience.*"

974. Asked if he joined a drug development team at an early stage, without a background experience in an enzyme, what he (as a skilled medicinal chemist) would typically do, Dr Edwards responded as follows:

> "[T]*alking to your team members would be important, biology, pharmacology, any team member that's already working on the project. They will have information on related topics like assays, animal models, the disease background that you can then learn from. Typically, you might also attend conferences to pick up information in the area. You might study the literature, particularly relevant to patents and publications and reviews in the area, which you may not have accessed before because you weren't working in that specific area....[T]hose are some of the ways you would pick up knowledge.*"

4.. Some Relevant Concepts

975. Noting that in his first witness statement, Dr Edwards discusses (i) enzymes and proteases from §6.5 onwards, (ii) the sequence of a substrate structure, and (iii) the features of Factor Xa as a serine protease and how it operates in the prothrombinase complex, counsel asked if Dr Edwards could identify and explain some of those concepts from the perspective of a medicinal chemist. To this, Dr Edwards responded as follows:

- "[a]*n enzyme is something which speeds up a reaction, in this case in the body, which, without the action of an enzyme, would be too slow to be useful otherwise. So, it catalyses the reaction, it speeds it up.*"
- as to "*competitive*" and "*non-competitive*" inhibitors:

  > "*there would be an active site, a binding site where the natural substrate would bind. So, a competitive inhibitor would also bind at the same site and it would need to out-compete the natural substrate to be effective. There are other sites, such as allosteric sites - these are different positions on the same protein, for example - where the inhibitor would bind, but they're not binding at the active site, so the natural substrate could still bind there at the same time. What they do is affect the shape of the target, so they alter that so that it doesn't function in the way that it should*."

- as to the concept of serine proteases and how they operate to cleave peptides and proteins:

  > "[T]*he inhibitor binds to the active site and there's a bond, an amide bond which is cleaved and in this case the serine protease, the hydroxyl of the serine, the amino acid that's involved in cleaving that scissile bond, as it's called, and that cleaves the peptide into a smaller fragment*."

- as to the role of potency in his work as a medicinal chemist,

  > "[T]*ypically if you're looking to generate inhibitors, which are potent against a particular target, so they either bind, have a high binding affinity so a low numeric value, in this case Ki's that we've heard about earlier today. So, they would be in the low nanomolar region for Factor Xa, for example. You have other measures of potency like an IC50, so reducing the activity by 50%. So, there are different measures for...understanding that. But I guess generally speaking it's how an inhibitor interacts with a particular target and the strength of that interaction.*"

- as to the concept of selectivity,

  > "[T]*here are related serine proteases which presumably are something you would need to avoid....*[O]*btaining selectivity in pretty much any project that I've worked on has been an important goal and there are a number of related proteases in the panel that you might consider and some of those are listed in the common general knowledge, the agreed document. So, it would be important to maintain a high level of selectivity. Anything between 100 and 1,000 fold is quite common across many, many targets*

and certainly with Factor Xa, you know, it wouldn't be unreasonable to have 1,000 fold selectivity against related targets that you don't want to interfere with."

[At this juncture, counsel for Teva noted §6.14 of Dr Edwards's first witness statement where he states that "*The similarity in amino acid sequence of substrate structure would mean that the skilled person would be disposed to think that a compound which inhibits factor Xa might or would also inhibit another serine protease.*" Counsel queried, as a general proposition, whether Dr Edwards would state that similarity in the amino acid sequence of substrate structure is something one needs to be conscious of in terms of selectivity. In response, Dr Edwards said, "*Generally, yes. There are effects on the homology of the pocket that we need to consider. So, you wouldn't look at this in isolation. But certainly something with a high sequence homology within a pocket, you may expect some degree of a similar shape, and therefore the potential to effect other targets if the homology is high.*"]

– as to fixing an inhibitor in a pocket, "*when an inhibitor sits in the pocket, in order to stay there and bind, it forms productive interactions. For example, 108(c) we're talking about hydrogen bonds. This is an alignment of a certain atomic grouping, so a proton, which would be a hydrogen bond donor, with an acceptor such as an oxygen atom. So, because there's a charge, an equal charge distribution across that you can get a binding event. A reversible binding event. And that helps to fix the inhibitor in the pocket.*"

– as to the shape of an inhibitor, "*The shape of the inhibitor is important because it needs to fit into the pocket and not, for example, provider steric clashes....*[I]*f there's a clash between the inhibitor and the amino acid residues lining the pocket, it won't fit, which is obviously not going to aid binding*."

– as to what a lactam is, "*a lactam is simply a cyclic amide, so an amide*". Dr Edwards also drew a diagram on a flip chart by the witness box, the following exchange then taking place between Dr Edwards and counsel for Teva:

Dr Edwards:	*If you're thinking about an amide, it has an arrangement of nitrogen atom connected to a carbon, double bond to oxygen. So, then you have cares groups coming off it. It is really that arrangement that's important (indicating). A lactam is the amide cycloid, so....you have the same arrangement with nitrogen and a carbonyl but now it's containing the other elements, so that is a lactam.*
Counsel:	*Just to identify, where is the lactam in that drawing, Dr. Edwards?*
Dr Edwards:	*So, I will circle the ring system which includes the nitrogen and the carbonyl exocyclic to the ring.*
Counsel:	*So, the carbonyl, as I understand it, is where...there's* [an] *outer cyclic ring and the two lines come out to join oxygen,*

	that's the carbonyl?
Dr Edwards:	*Yes. From carbon to oxygen is a double bond.*
Counsel:	*And then the addition of the nitrogen then at the next corner, that makes it a lactam, is that correct?*
Dr Edwards:	*Yes*.

– as to the significance of a lactam in medicinal chemistry:

> "[I]*t's a relatively common group. It's simple. It contains some potential for changing the electron distribution and so that could mimic other groups, sulfones, for example, different heteroatoms. It can also form productive interactions with the amino acids lining the pocket. It's relatively small. It has...he capability to mimic phenyl rings, aromatic rings, for example.*"

– as to what a phenyl or an aromatic ring is, Dr Edwards returned to the flip-chart and indicated as follows:

> "*In this case – phenyl – it is six-membered ring, all carbon atoms. It forms a cycle and it has three double bonds which overlap to form a pi cloud so it's electron rich. It can react with areas of electron deficiency, for example, in proteins. One of the interactions on (g) was pie interaction so you can get what's called edge-to-face or pi/pi stacking interactions, depending on the electron density within the rings. So, that's a very common fragment within drug discovery. The lactam is also a six-membered ring, it's not plainer* [sic- planar?] *as the phenyl group is. But it could be thought of as a replacement. Particularly, for example, if you have a heteroatom and you were inventing a pyridine with a nitrogen instead of one of the carbons, you can see some greater level of overlap between the two structures.*"

– as to whether all lactams necessarily six-membered, "*They could be four-membered and above really but five, six and seven are probably the most common ring sizes that you will see in drug discovery.*"

– on the issue of whether there are other substituents that can bond into the pockets of a target enzyme, Dr Edwards indicated that there were many other such substituents:

> "*If you think about the typical range of heteroatoms that you may have used in drug discovery, so you might have nidogen, oxygen, sulphur, those are typical atoms, along with carbon. You can arrange those in many different ways. So, there's dozens and dozens of potential groupings that you could replace any one group with, in theory. Not all will work but there's a large range.*"

– as to whether medicinal chemistry is not predictable, in terms of being able to predict what the impact of changing structure is:

> "*It's not wholly predictable....It depends on what you're predicting for. In this case, I guess, of most relevance to Factor Xa would be for example, potency. So, if you were to change the structure, it's*

not possible to predict, with any accuracy, the exact value of Ki you might expect. And even small changes can have the big effects in terms of the potency - positively or negatively."

5. Factor Xa

i. Factor Xa and pockets

976. Given that Dr Edwards had identified how enzymes have different pockets where the substrate can bind, counsel asked if he (Dr Edwards) could describe how Factor Xa fits within that arrangement. To this, Dr Edwards responded as follows:

"[T]*here are two main areas, two pockets that are of interest termed S1 and S4 and the common general knowledge indicates that the spatial arrangement of groupings that enter those pockets needs to be in an L configuration. So, you need to be spot on really to optimise interactions within those pockets. So, S1, for example, has hydrophobic walls, it's relatively narrow, and takes in basic groupings and that's how, I guess, early inhibitors started in terms of design....An S4 is perhaps a little more tolerant of groups that can be bound within it and interact. And potentially specificity can be gained from that S4 pocket, for example.*"

977. Asked whether there are other pockets or other binding sites in Factor Xa, Dr Edwards indicated that "*I think there are surface areas. So, it doesn't have the same pockets S2, S3 that thrombin has, for example, so you may look for surface interactions with a Factor Xa inhibitor.*"

ii. Potency of Effective Factor Xa Inhibitors

978. Asked, from his understanding of the common general knowledge in 2001 and from his research, what level of potency was then being sought for effective Factor Xa inhibitors, Dr Edwards said "*Certainly low nanomolar, single digit nanomolar or high picomolar potency was achievable in some inhibitors and to my mind that is where the industry expected to find useful compounds.*"

979. Counsel for Teva noted that in his witness statement, at §§6.21-6.23, Dr Edwards sets out three particular reasons for nanomolar potency, Dr Edwards said as follows:

"[H]*igher potency can translate into a lower dosage which means cost of goods, for example, is smaller, particularly if it's a difficult compound to make. And, also, importantly, potency is an important parameter and it feeds into efficacy of the drug. It's not the only parameter that's important, it's one of them. But, if you have a suboptimal property somewhere else, oral bioavailability for example, or selectivity, if you have a really potent compound it offsets, to a degree, the issue you have somewhere else. So, it's desirable to be potent. You need to think about your efficacious dose and what level of potency you need to achieve that. And from that the level of increasing dose for toxicity studies you need. So, if you're not particularly potent, you're going to need huge amounts of compounds in your tox studies which are likely to be not tolerated. So, it's better to be more potent, generally speaking.*"

980. Noting that the proposition that one would be searching for potent drugs is not in dispute (it is reflected in numerous places in the agreed CGK document), counsel asked what, as a medicinal chemist engaged in drug discovery, Dr Edwards would need to see and would expect to see to understand that a compound has the potency one is expecting and looking for? To this, Dr Edwards answered that "*I think you need the right assays in place to start with but you'd also need to see data. The closed loop is design, synthesise and screen. And screen means understand the data, obtain the data and then use that data to inform the next iterative cycle. So, you need to see data.*"

6. High throughput screening

981. Noting that §111 of the agreed CGK document discusses the starting point for a project, which includes high throughput screening, counsel for Teva asked Dr Edwards to explain his understanding of high throughput screening and what it involves.

982. (Paragraph 233 of the agreed CGK document states as follows, under the heading "*Starting point*":

> "*The skilled medicinal chemist would often first become involved in a new drug discovery project once the biological target had been identified. Their first task would be to work with the skilled pharmacologist to identify a compound (or class of compounds) as a starting point for the project (in this case potential inhibitors). The objective would be to find a compound or compounds with sufficient activity against the target, and possibly selectivity for that target over other enzymes, which could form a starting point for synthesising analogues, which may have improved properties. Starting points can typically be identified in three different ways: i) finding known compounds published in the literature; ii) starting from the endogenous substrate; and iii) high-throughput screening, which was already in use in 2001, and in which tens or hundreds of thousands of compounds can be screened using automated assays*").

983. Dr Edwards explained his understanding of high throughput screening and what it involves in the following terms:

> "*That was one technique used to generate compounds of interest very early stage hits. So, at that time, the late nineties onwards, the pharmaceutical industry was gearing up to perform biological screens on up to a million, typically a million compounds. The big companies, certainly Pfizer, would screen routinely a million compounds in their screening deck as they called it. So, it's a collection of curated compounds that the company owns, some of which have been made in-house, some of which have been bought in. The assays typically are developed in the lab and maybe low throughputs, a few compounds a day, which obviously if you're screening a million compounds is doesn't work. So, you have to have ways of screening, typically then in 96-well plate, so a plate containing 96 compounds. That was worked up to 384 compounds and so on. So, biologically the particular assay you were interested in, in this case most relevant Factor Xa would be screened, would be used to screen a million compounds or thereabouts. And a list of data would be produced which would include some active compounds. Of the million, sometimes you get nothing and I've worked on programmes where we got zero hits and sometimes you get several thousand hits. It really depends on the forgiveness of the target. So, you may have 3,000 hits and....*[i]*t's too many compounds to work with so you need ways of coping with that number. So, you may look to group the hundreds or thousands of compounds together in a series....*[Y]*ou would look at the structure and group them based on similarity. And you could say in this series there's some SAR because we know analogues, close analogues are showing activity. And that gives you a little bit more confidence that the hits are real because you've got more than one hit structurally related. You would always make some of the compounds or all of them, depending on how many you have, as fresh samples to prove that the activity is real and not derived from an impurity in the screen. You may also have singletons, so a single compound with no related structures. What you would do there is generate some very close analogues making a single change, for example, and test to see whether they are active. If there's no activity, probably that was a false positive and not of interest. If you generate activity in closely-related analogues, again you potentially have another series to work on. So, if you're fortunate you'll have a multiple series that you need to think about and decide*

which ones am I taking forward? ...[A]*t that stage you may have hits, which are very, very early stage compounds in the screening cascade. So, you've got some very basic activity – 10 micromolar, for example, and that's a typical read-out in terms of potency for an HTS. Then you would work on determining how many series you can take forward and determining which series are more interesting. For example, if you determine that from the potency it tracks for a property like lipophilicity and you need more lipophilic compounds to be active that tends to be* [a] *bad thing because you're going to get two lipophilic compounds that you can't do anything with and are not going to make good drugs....*[I]*t may be a series falls out because of a property tracking that you don't want. So, you use various techniques to whittle this down to a manageable number of series or compounds that you can work on and further optimise and hit to lead.*"

984. Counsel asked Dr Edwards to confirm that in the just-described process "*you need to have confidence the hits are real and you need proof of the outcome because there can be false hits and impurities*". Dr Edwards confirmed that this was so.

7. Selectivity – I

985. Counsel for Teva noted that Dr Edwards had mentioned trying to find data through this high throughput screening of the libraries and asked if her understanding was correct, that "it's not just potency but also selectivity you're testing for". In response, Dr Edwards indicated that this was so, "*You'd also test for cell toxicity early on. So, if the compounds are toxic to certain cells that's a red flag and you wouldn't necessarily want to take them forward. The HTS screening cascade has the widest number of compounds against the primary target and then you take the smallest set against toxicity, for example, to ensure that that's not an issue in the cell type that you're looking at, as well as selectivity.*"

986. Counsel for Teva asked Dr Edwards to "*explain selectivity, perhaps, in terms of medicinal chemist work, what would you be looking for and what actual information would you need in terms of selectivity?*". To this, Dr Edwards responded as follows:

"*You would need to see the data but it is very, very project-specific and this – the exact levels of...*[cut-off] *would be discussed in the project. So, for example, a tenfold selectivity against a particular target might be enough to be of interest in the hit phase. And that obviously needs to be built up in terms of full selectivity as you move forward. It could be that you really need to avoid and certain target and you might immediately set 100-fold. You it really just depends on the project. The compounds at that stage are so early you know there are issues you've got to work on, so, it's a discussion to be had at the time as to where you set your selectivity level, but it wouldn't be 1,000-fold, for example, at that stage, necessarily.*"

8. Assays

987. Noting that there is engagement and iteration as one works though the drug discovery process, counsel asked what, as a medicinal chemist, one would need in order to go forward with the process. To this, Dr Edwards answered as follows:

"[R]*eliable assays, you need those set up, enough separate assays such as ADME/DMPK that we've look [sic?] talked about looking at solubility, lipophilicity there and whether it hits cytochrome P450....*[T]*here's a whole array of other assays, in addition to potency and selectivity that would come into play – not necessarily all K1[sic- Ki?] were these very early compounds but as they pass through certain stage gates they become more interesting, you test them in more assays to see how good/bad they are. So, you need the assays in place and the expertise in the team to help evaluate*

the data that you're getting but it is important to get the data."

9. Selectivity – II

988. Returning again to the issue of selectivity (in the context of Factor Xa) counsel stated, "*I think you say in your witness statement...that there's particular similarity in amino acid sequences of the substrate structure that would make you disposed to think that a compound that inhibits Factor Xa might also inhibit other serine proteases. Can you expand on that..?*" To this, Dr Edwards responded as follows:

> "[I]*f the amino acid sequence within the pocket is very similar, there is a possibility that a particular inhibitor showing activity of Factor Xa could also show activity and related serine that we have in the panel. So, it is something to be careful of and it is something to track the particular off targets that you're looking to avoid through the programme. And you would do that constantly. You wouldn't necessarily abandon selectivity after you've shown that you're happy with the first few compounds. It's an important parameter to measure against your set of targets you're looking to avoid.*"

989. Noting that Dr Young had stated in his second witness statement at §21 that Factor Xa inhibitors that were potent tended to also be selective, counsel for Teva asked Dr Edwards for his view of that statement. To this, Dr Edwards responded as follows:

> "[T]*he issue is how selective is selective? It's certainly the case that you wouldn't stop measuring selectivity against a potent compound. You cannot necessarily predict with a new compound that is designed and not tested, before it is tested, what the level of selectivity will be. And a lot of the common general knowledge that we see assumes that the X-ray structure, and even to a lesser degree the homology model, which is a best guess at what they might look like, are static. And we know that often they're not. I've been involved in a programme where we introduced a specific substituent composition and the protein flexed, changed its shape and opened up a new binding pocket allied to where we were. So, proteins are not static, they do flex. So, there is a theoretical possibility that any new inhibitor could induce a change in the pocket, which could alter the level of selectivity. So, it's an important parameter to measure, as you're going along*."

10. Modifications

990. Counsel invited Dr Edwards to comment on the observation in the agreed CGK document (§118) that "*Often relatively small modifications can result in significant changes in activity against the target enzyme or against other enzymes*". In this regard, Dr Edwards observed as follows:

> "[T]*hat is true. There are a number of examples in the literature and it's certainly the case with Factor Xa that a small modification can change the binding mode, even a large change can change the binding mode. We know in Factor Xa that sometimes there's a flip, groupings that you would expect to bind in S1 bind in S4 and vice versa. And that can't be predicted. So, you can design an inhibitor, expecting [it] to be active but suddenly you find that it doesn't bind in the way that you expected. Very small changes in structure, for example, the addition of a fluorine, addition of a methyl group. A change of a heteroatom can have a huge effect on the parameters you're interested in, whether that's primary potency, say, and there are a number of examples out there that demonstrate this.*"

991. Counsel noted in passing that "*Dr Young agrees with us...in his* [second] *witness statement at paragraph 23...that small changes can have material effects.*"

992. Asked if it remained his evidence, as stated at §6.31 of his witness statement that "*The skilled medicinal chemist would always need to test a new compound's potency and selectivity when they have made changes to the chemical structure. Small, single, changes in structure can have a large effect on potency and/or selectivity*, Dr Edwards indicated that it did.

11. The 'Magic Methyl Effect'

993. Counsel for Teva asked Dr Edwards to explain the 'magic methyl effect'. Dr Edwards did so in the following terms:

> "*I guess, in general, it constitutes a very small change. The addition of a methyl group, a particular position within an inhibitor, for example, can have a drastic change on the potency, usually you would look to see an increase in potency but it would be unexpected. So, that's a very small change, potentially, with a very large effect.*"

12. Inhibitors of Factor Xa

994. Asked if there is any established rule about how he would expect an inhibitor of Factor Xa to bind, Dr Edwards indicated that "[T]*here are some general principles but it's not a hard and fast rule. Early stage inhibitors tended to have strongly basic centres to bind into S1 but they were proven to be replaceable. So, I think it's impossible to be certain how a compound will bind and predict accurately its potency without testing it.*"

995. Asked by way of follow-on question whether the compound's structure would allow one to have any reason to believe what the potency would be if the structure was changed, Dr Edwards indicated as follows:

> "*You could hope that you're finding activity. So, if you have an established series and you make a particular example within that series, so...a very small change in a very well-documented series...for example, if you had a methyl, an ethyl and a butyl group and you want to make a propyl analogue, so you're just extending the chain by one carbon atom each time, and you have three of the four data points, let's say, up to the butyl, you might be confident that the propyl analogue will have some level of activity. You couldn't be absolutely sure as to the numeric value but you'd be fairly confident, I think, that you could find activity there. If you're making a change, or cyclising or you're replacing one group with another, I think the expectation and the level of confidence you would have that you would get activity is reduced, because it's maybe an extrapolation rather than interpolation. And that would be harder to be sure and certainly predict numerically what the Ki would be.*"

13. Rigidification

996. Counsel noted that Dr Edwards had outlined a range of different changes that could have an impact on the inhibitory effect of an inhibitor, one possibility being rigidification (addressed in the agreed CGK document from §§115 to 116. She asked Dr Edwards to read §§115-116 and then make comment. §§115 and 116 of the agreed CGK document state as follows, under the heading "*Optimisation*":

> "115. *One strategy the skilled medicinal chemist could try in an attempt to improve the activity of a given compound (which would result in the formation of a new compound with a different chemical structure to that of the original compound) and reduce its side-effects is 'rigidification'. One well-known method of rigidifying a flexible molecule is to incorporate the skeleton of the flexible molecule into a ring system (cyclisation). Flexible side chains can*

also be rigidified by incorporating a rigid functional group e.g., a double bond, alkyne, amide or aromatic ring....

116. *Less flexible inhibitors can result in stronger binding, and cyclisation was a common way of making less flexible compounds in 2001. However, the outcome will depend on whether the conformation that the compound is 'locked' into is one that is favoured for binding. If it is, rigidification will increase the strength of binding; the reduction in the number of conformations may also reduce interactions with other enzymes or receptors and hence improve selectivity. However, rigidifying an inhibitor could also have the opposite effect, since the inhibitor could be locked in a conformation that is less favourable for binding, thus reducing binding affinity or even eliminating binding altogether.*"

997. Having read the just-quoted paragraphs, Dr Edwards stated as follows:

"*I agree with that. It is a well-known tactic in drug discovery to alter the potency in your favour. It certainly can work and there are many examples where it does. It can also fail and one of the things, let's say, with reference to Factor Xa you have this L configuration and P1 and P4 binding into S1 and S4. The spatial relationships needs to be spot on to make the optimal interactions. So, cyclising a particular template may work if it's precise and gives you exactly what you need. But no doubt there are a lot of attempts to generate different cyclic cause which fall because ultimately they position the group slightly wrongly, slightly imperfectly. So, it's a valid strategy but it can fail as well.*"

998. Asked expressly if he agreed with the observation in §116 that "[R]*igidifying an inhibitor could also have the opposite effect, since the inhibitor could be locked in a conformation that is less favourable for binding, thus reducing binding affinity or even eliminating binding altogether*", Dr Edwards indicated that he did.

14. The Patent Application

i. What the Inventors Were Trying to Achieve

999. Turning to the 652 application, counsel for Teva asked Dr Edwards, from his reading of the document, what the inventors were trying to achieve. His response was "*Therapeutic Factor Xa inhibitors.*"

ii. Information Establishing that Inventors Found Effective Xa Inhibitor

1000. Asked if he was to see the information that he would require to be satisfied, as a skilled medicinal chemist, that the inventors had found an effective Factor Xa inhibitor, what he would need to see, Dr Edwards indicated that he would need to see "[d]*ata actually ascribed to compounds within the patent so that as someone who is not involved with the patent but someone interested in the field, like a competitive company, for example, I'd be wanting to see activity against a range of compounds to build some SAR* [Structure-Activity Relationships]. *So, there must be data ascribed to compounds within the pack.*"

1001. Asked by counsel for Teva whether "*at the high level, did you see what you would have wished to see in this patent application?*", Dr Edwards responded "*No, I could see no data ascribed to any compound.*"

iii. Presence of Lactam in Potential Factor Xa Inhibitor

1002. Noting that in his first witness statement (at §7), he goes through the patent application and describes different aspects of the patent application and that at §7.3 Dr Edwards observes that "*The skilled medicinal chemist would therefore not be surprised that a lactam is included in a potential Factor Xa inhibitor*", counsel asked Dr Edwards to explain this observation. At this juncture the following exchange occurred between Dr Edwards and counsel:

Dr Edwards:	*It's a very standard grouping. There's nothing special about it particularly, nothing unusual. So, it would be within the mind of a medicinal chemist as a particular grouping that may be included in inhibitors. So, I guess, along those lines it's a perfectly common example of something you may find in an inhibitor.*
Counsel:	*And...in the following paragraph, you...address the question of whether the lactam would be located. Can you explain your view in that paragraph please?*
Dr Edwards:	...[L]*ooking at the patent, the core itself has a lactam ring, as well as a second position, I believe. So, it wasn't immediately clear to me where any lactam may reside.*

iv. Application 652

1003. Turning to p.6 of the application, counsel asked Dr Edwards whether there was any information on that page that you would see of interest to a skilled medicinal chemist. To this, Dr Edwards responded that "[T]*here's some general text on efficacious and specific inhibitors of Factor Xa, some general points a to g that would be useful, these are very generic points. I don't see in that section of the text any data or any indication of what may be particularly interesting.*"

v. Markush Formula (Application 652)

1004. Leading Dr Edwards next to p.8 of the 652 application, counsel for Teva noted that there is a Markush formula at the top of that page and asked if Dr Edwards could explain "*what that means and...how you can extrapolate a compound from the listing there at the very top of page 8*". The following exchange then occurred between Dr Edwards and counsel for Teva:

Dr Edwards:	"[I]*t's a generic representation of a range of compounds and a range of fragments and structures within it. So, here it's* P_4*-P-M-*M_4 *and each of those terms Ps and the Ms represent certain groupings, certain fragments that are linked together. As you go through the following pages, in this case it's one an embodied, it defines what each of those groupings could be.*
Counsel:	*As I understand it, each of* P_4*, P, M and* M_4 *are then further defined as you go through the document, is that right?*
Dr Edwards:	*Yes, into separate or preferred embodiments.*
Counsel:	*How many compounds would be captured by that Markush formula at the top of p. 8? ...*
Counsel:	*Incalculable billions, trillions. I don't know. It's a huge number.*

vi. Compound 18

1005. Having elicited from Dr Edwards that he read the 652 application "without any hindsight or any information", counsel for Teva then asked Dr Edwards whether "*when you read this document, did you identify any particular compound from among the, as you say, incalculable number of compounds covered as being of interest?*" The following exchange then ensued between Dr Edwards and counsel for Teva:

Dr Edwards:	*Not a specific compound, no.*
Counsel:	*But you now know, as I understand it, that apixaban is the compound of interest?*
Dr Edwards:	*Compound 18, yes.*
Counsel:	*And...can you identify apixaban...Dr Edwards...from the embodiments?...*
Dr Edwards:	*Only with the benefit of hindsight, knowing its structure....*
Counsel:	*Can you identify if apixaban is actually drawn out or written out in this patent application, if you have 652 in front of you?...*
Dr Edwards:	*I don't see the actual structure of compound 18 drawn out....*
Counsel:	*Well...if my friend does not mind me leading you...*[if] *I could point your attention to the bottom of page 69...I understand...that this is the compound known as apixaban, is that correct?*
Dr Edwards:	*Yes.*
Counsel:	*That would be your own understanding, thank you. And there are, in the patent application, as I understand it...15 embodiments and the embodiments continue right through, as I understand it, until page 129. Does that accord with your understanding of the patent application?*
Dr Edwards:	*Yes....*
Counsel:	*There's 15 embodiments. Do you have any idea how many compounds are potentially encapsulated by those embodiments? ...*
Dr Edwards:	[J]*ust in the embodiments? I don't know. Huge numbers, millions, billions. It would take a long time to calculate*.

vii. Belief in Reason for Due Inhibition of Factor Xa or Thrombin

1006. Counsel for Teva led Dr Edwards to p.169 of the 652 application, where it states that "*The anticoagulant effect of compounds of the present invention is believed to be due inhibition of factor Xa or thrombin"* and asked Dr Edwards to give his interpretation of that line of the patent application. To this, Dr Edwards responded as follows:

> "*It's somewhat confusing if the patent [is] directed towards factor Xa inhibitors. I note from Dr Young's witness statement that he contends that the industry at that time was searching for dual inhibitors, but I could not identify, in the common general knowledge documents that we have, or the document that was agreed previously, any notion of search for dual inhibitors. So, it's not clear to me why, in this particular patent, an inhibitor of thrombin would be important and indeed which compounds were inhibitors of which target, if any.*"

viii. Chromogenic Assay

1007. Turning to the description on p.169 of a chromogenic assay, counsel for Teva asked Dr Edwards to give his view of that description. To this, Dr Edwards responded as follows:

> "*I'm not an expert on this assay itself, I can only give a generalist opinion as a medicinal chemist who may have a working knowledge. It's a very standard assay, there doesn't seem to be anything out of ordinary or novel in terms of what is here and I understand it to be a commercial kit that you can buy in for the assay. So, I'm not an expert, but I don't believe there's anything unusual there*."

1008. Asked to explain the role of the mentioned chromogenic substrate (S2222 – a substrate that he did not recognise but which he presumed to be a synthetic substrate, rather than extracted from a natural product), Dr Edwards observed as follows:

"[I]*t's a marker of, whether it's hydrolysed or –I guess the fluorescence potentially of the compound changes whether you have an inhibitor which is active or not. So, it's a marker for how active the compound may be in the assay....I haven't studied that in any detail so I'm not an expert.*"

ix. Tested Compounds, *etc*.

1009. Counsel turned next to the following observations at p.170 of the 652 application:

"*Compounds tested in the above assay are considered to be active if they exhibit a Ki of ≤ 10 μM. Preferred compounds of the present invention have K 's of ≤ 1 uM. More preferred compounds of the present invention have Ki's of ≤0.1 μM. Even more preferred compounds of the present invention have Ki's of ≤0.01 μM. Still more preferred compounds of the present invention have Ki's of ≤0.001 μM. Using the methodology described above, a number of compounds of the present invention were found to exhibit Ki's of ≤10 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors* ."

1010. Asked what the just-quoted text conveyed to him as a skilled medicinal chemist, Dr Edwards responded as follows:

"[T]*he initial sentences are fairly standard, found in many patents, because they're just partitioning activity within log ranges. And then it goes on to describe: 'A number of compounds of the present invention were found to exhibit K_is of less than 10 micromolar, confirming utility.' I believe in Dr. Young's witness statement he indicates that a K_i of 10 micromolar is not an effective factor Xa inhibitor. So, I wouldn't agree with that. Anything with a K_i of 10 micromolar is very much a start point, maybe an output from a high throughput screening, or other. It is certainly not indicative of an efficacious factor Xa inhibitor or an effective inhibitor.*"

1011. Counsel turned next to p.172 of the patent application There, following a description in the preceding paragraphs of a chromogenic assay in respect of thrombin inhibition, the following sentence appears: "*Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a Ki of less than 10 μM, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.*" Asked what this sentence conveyed to him, Dr Edwards responded that it conveyed to him:

"[t]*hat some or all of the compounds have activity against thrombin. It's known which compounds and how many. And given the bracket the K_i is put into, they would be potentially as effective and as potent as the factor Xa inhibitors. There's no data to indicate they're more or less active than factor Xa*".

1012. Asked by counsel for Teva whether the texts "*that we've looked at*"

- "*tell you which compounds were tested for either factor Xa or thrombin inhibition*", Dr Edwards's response was "*No, there's no data ascribed to the compounds for activity at thrombin or factor Xa to be able to determine whether they were dual inhibitors, or inhibitors of one target alone.*"
- "*give you a specific reason to believe that there is credibility to the assertion that they're effective factor Xa inhibitors in this patent*", Dr Edwards's response was "*No, the bracket the K_i is put into, less than 10 micromolar, is, as I say, a start point. It certainly wouldn't be a level of potency that would provide any effective inhibitor*."
- "*give you any information as to which compounds were tested for thrombin*

inhibition and have K_is of less than 10 micromolar for thrombin inhibition", Dr Edwards' response was "*No. To me, there's no information for any of the compounds in terms of activity and potency to understand which compounds are active in thrombin.*"

x. Rabbit Shunt Model

1013. Counsel turned next to the consideration in patent application 652 of a rabbit shunt model, and drawing Dr Edwards's particular attention to the related observation in the application that "*The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model*". Asked whether this text gave Dr Edwards "*any information of use to you as a medicinal chemist*", Dr Edwards indicated that it did not.

xi. Testing and Output of Testing

1014. Counsel for Teva asked Dr Edwards to confirm (i) "*from your review of this patent application...what data there is...to indicate the actual carrying out of any tests and the output of the carrying out of any tests*" – to this Dr Edwards responded "*There's none*"; (ii) that the only two tests "*we have identified*" are those tests on pp.170 and 172 – to this Dr Edwards responded "*Yes*".

xii. The Exemplified Compounds

1015. Counsel turned next to look at the exemplified compounds in application 652. She brought counsel first to Example 14 and asked Dr Edwards to give an overview of the type of synthesis exercise that he thought was carried out and its complexity or otherwise. The following exchange ensued between Dr Edwards and counsel for Teva:

Dr Edwards:	[F]*rom my read of the patent, all of the reactions and...typical synthesis reaction schemes...were given earlier in the patent...*[and] *are very standard, common at the time, there's nothing unusual or novel in the synthetic endeavours. Looking at this particular compound and counting the number of parts, there's...potentially nine steps....That is...well within the remit of a medicinal chemist in terms of synthetic complexity. It should be noted that...in the early stages of drug discovery, particularly in a medicinal chemist's hand...the overriding goal is to produce the compound in sufficient quantity to enable primary potency testing, in this case...Xa. You don't know that the inhibitor that you have designed and synthesised will be active, so there's no point in spending, potentially, months optimising a route to minimise the number of steps, minimise potentially reactive intermediates that are dangerous, optimising yield, to have a beautiful synthesis of an inhibitor that then turns out to be inactive, or given the length of time it's taken to synthesise is, it the SAR has moved on in other aspects and your compound becomes worthless. So, the idea in medicinal chemistry is to get the compound as quickly as possible. So, the yields may be low and that's accepted. You just need to produce enough compound. And the number of steps here, given the normality of the chemistry is not an issue for a typical discovery programme.*
Counsel:	*So that's...steps A to I in this particular example...right..?*
Dr Edwards:	*Yes.*
Counsel:	*And each step indicates the synthesis of a different substituent perhaps of the compound..?*
Dr Edwards:	*An intermediate en route....*[Y]*ou're building elements of the final*

compound. You're including them into a structure that gets elaborated more and more up to the final compound....

Counsel: *And just turning to the final section of that example on page 215...there's some letters there that it would be perhaps helpful if you could explain....One of them...is 'LC/MS'...*

Dr Edwards: '[L]*iquid chromatography mass spectrometry*'....[whereby] *you're looking in that spectrum for a peak that corresponds to your molecular ion....*

Counsel: *And the 'NMR'..?*

Dr Edwards: [That's] *'Nuclear magnetic resonance'....a technique invented...in the fifties by physicists to determine structures. So, in this case the compound is dissolved in deuterated DMSO, which is a deuterated solvent. Deuteration means there are no protons which appear in the NMR spectrum, that's what you're looking for. And it would swamp the spectrum. So, the solvent is deuterated and then you have the delta which is the shift from zero for a number of peaks. So, these are ascribing – each peak is ascribed to a structural element, for example....*

Counsel: ...[T]*urning to page 225...*[what is] *HRMS...?*

Dr Edwards: *'High-res mass spectrum'....*[T]*hat....confirms the molecular structure....*[I]*t's a way of confirming the compound is present.*

Counsel: [Does]*...the information...given to you by these pages of the patent application...give you any indication of any structural attributes of the compounds in question?*

Dr Edwards: *Structural attributes? Yes, they should do. So, the NMR particularly is informing, identifying peaks and ascribing that to structural elements. So, you can see the title, you could work out the structure and then assign the NMR spectrum to it.*

Counsel: *And does it tell you anything about the effectiveness of the compounds?*

Dr Edwards: *No*.

xiii. Dr Young's Six Reasons for the Plausibility of Apixaban

1016. Counsel for Teva turned next to the six reasons offered by Dr Young as to the plausibility of apixaban as an effective factor Xa inhibitor, with the following exchange taking place between counsel and Dr Edwards:

"[1. P_1-core-P_4 structure]

Counsel: [T]*he first proposition...is that apixaban has the P_1-core-P_4 structure that was common to known factor Xa inhibitors....*[Dr Young] *says:*

> *'Apixaban has neutral P_1 and P_4 groups and the skilled person would know that factor Xa inhibitors with neutral (or weakly basic) P_1 and P_4 groups were an area of particular interest (for the reasons that I give above) and that several factor Xa inhibitors with neutral or weakly basic groups had been shown to be effective as anticoagulants and in animal models.'*

...I don't think you dispute that statement..?

Dr Edwards: *In general, yes, it's true.*

[2. Methoxyphenyl and S_1 binding]

Counsel: ...[T]*urning to the second reason that Dr. Young relies upon for asserting the validity of the patent...:*

> *'Apixaban has a methoxyphenyl group in the P_1 position. As I describe at paragraph 48 above, methoxyphenyl substituents had been shown to bind in the S_1 pocket of factor Xa through modelling and inhibitors with methoxyphenyl as both P_1 and P_4 motifs had shown factor Xa activity.'*

....[I]*n paragraph 48 he said:*

> *'Lilly's identification of the (pyridin-4-yl)piperidine/methoxybenzamide combination...presented an early example of a reduced basicity compound (pKa - 10.88), which was modelled to bind to factor Xa with the methoxy phenyl in the S1 pocket. This was contrary to a reported hypothesis that Example 4 (described below) was likely to bind with the pyridine in S1 in an otherwise neutral structure and consistent with the commentary of Zhu and Scarborough at paragraph 45 above.'*

He then says...

> *'The significance of this molecule and/or closely related examples in the series were noted in Maignan, Ries, Zhu 2000, Zhu 1999, Betz and Rai...'*

....And if you would just look at the drawing there in Figure 9 of his witness statement...it might be useful if you would explain to the Court what methoxyphenyl means, to start with?

Dr Edwards: ...[I]*f you look at the structure, the very top ring, six-membered ring, you have an oxygen and then a bond coming off it, which actually finishes in a CH_3 group. So, that's the methyl. The oxygen makes it methoxy and then attached to the six-membered ring is the methoxyphenyl. So, that's the fragment. And then that itself is attached to an...amide linkage.*

Counsel: *Thank you. And what does the 4 in the 4-methoxyphenyl signify?*

Dr Edwards: *It means it's in the 1/4 position to the substituent, the amide. So, if you were to count the ring carbon of the six-membered ring as 1 and then count either way, 2, 3, 4, at the 4 position is the methoxy group....*

[a. Zhu]

(Zhu, B. and R. Scarborough, "Recent Advances in Inhibitors of Factor Xa in the Prothrombinase Complex" (1999) 1(1) *Current Opinion in Cardiovascular, Pulmonary & renal Investigational Drugs* 63-88)

Counsel: *You address this aspect of Dr. Young's evidence in your second witness statement....*[a]*nd you say in paragraph 1.24.1 that this article by Zhu...'....does not show the member which Dr. Young has*

selected as Example 2. Instead, it identifies the 4-chloro analogue with the piperidylpyridine substituent.'

Dr Edwards: *Yes...a number of these cited papers...indicate the 4-chorlo analogue as being preferred....*

[b. Betz]

(Betz, Andreas, "Recent Advances in Factor Xa Inhibitors" (2001) 11(6) *Expert Opin. Ther. Patents* 1007-1017)

Counsel: *At paragraph 1.24.2....I think what you're saying there is that while Betz does deal with compounds from the Lilly series, including five compounds, it doesn't identify the one that Dr Young relies on, is that right?*

Dr Edwards: *Yes.*

[c. Rai – I]

(Rai, R. *et alia*, "Perspectives on Factor Xa Inhibition" (2001) 8 *Current Medicinal Chemistry* 101-119)

Counsel: ...[A]*t paragraph 1.24.3 you note that Rai also identifies a selection of the compound from various companies, one...a Lilly compound*[,] *but it again is not the one that Dr. Young relies on and cites that article as support for, is that right?*

Dr Edwards: *Correct.*

[d. Ries and Priepke]

(Ries, Uwe and Henning Priepke, "Factor Xa Inhibitors – a Review of the Recent Patent Literature" (2000) 3(12) *IDrugs* 1509-1524)

Counsel: [Then there is]*....an article authored by Uwe J Ries & Henning Priepke?...*

Dr Edwards: *It's a review article. It encompasses, diligently, many examples at the time that had been reviewed in the previous 18 months or so.*

Counsel: ...[P]*age 1518 of the article is the most relevant one for the purposes of addressing the point that Dr. Young seeks to make. I think the heading begins: 'Neutral factor Xa inhibitors.' ...*

Dr Edwards: *So, I guess the bottom of the left-hand paragraph...[reads] 'This interesting neutral class of inhibitors...'[.] So that's of interest that they are not necessarily basic. '...may have the advantage of higher oral bioavailability...'*[.] *Then in the next paragraph: 'The most prominent series of neutral FXa inhibitors is described by researchers at Eli Lilly [48-50,150-152]. The starting point of their optimization program was the 1,2-bisbenzamidobenzene 54.' So, that's how they began their exploration. And that was a screening kit for them....*[T]*hey say that according to their binding model the methoxyphenyl occupies the S_1 subsite.*

Counsel: ...[T]*hat is the methoxyphenyl substituent occupying the S_1 site of the compound, is that correct?*

Dr Edwards: *Yes....*[I]*n this paper it would be the right hand one, because they...go on to say...'The left-hand methoxyphenyl group points into the S_4 subsite.' So, that must be the one on the left....*

Counsel: ...[T]*he figure that's drawn there at Figure 14 of that article, as I understand that Eli Lilly compound, it has two methoxyphenyl substituents, is that right?*

Dr Edwards: *Yes.*

Counsel: *Both binding the S_1 and the S_4 pocket?*

Dr Edwards: *Yes....*

Counsel *And it states... 'Extensive SAR studies revealed that the methoxy group on the right phenyl ring could only be replaced by small lipophilic groups, such as chlorine or vinyl'....And then it continues at the bottom of that paragraph to talk about greatly improved potency with inversion of one amide group....I might just ask you to go back to the figure on Figure 14. There's other Lilly compounds identified there?*

Dr Edwards: *Yes.*

Counsel: *Do they have methoxyphenyl in the S_1 pocket?...*

Dr Edwards: *57 has a methoxyphenyl, but it's unknown...whether that grouping would bind into S_1. We know that there's the potential for flipping, so that could bind into S_4. Just by looking at the structure, you couldn't be sure. And looking at the others, it's only 54, 55 and 57 that have that grouping.....*

[e. Replacement of 4-methoxyphenyl]

Counsel: *Then there's a line saying: 'In agreement with the proposed binding mode, substitution of the right 4-methoxyphenyl fragment in 54 by the 3-amidinophenylgroup furnished highly active amidine.' Can you comment on that?*

Dr Edwards: *...Yes...they've replaced the 4-methoxyphenyl with a basic centre, with a basic group. So, it may be anticipated there's some potency there. But what it does imply is that the 4-methoxyphenyl group is not key, it can be replaced with other groupings.*

Counsel: *Then...there's a sentence that says: 'Interestingly, the interchangability of 4-methoxyphenyl and 3-amidinophenyl substituents in the S_1-pocket was independently reported for phenylpyrazolecarboxamides by DuPont, although this company clearly started from the amidine series.' Does that give you any information...*[as] *to the significance of 4-methoxyphenyl in the S_1 pocket?*

Dr Edwards: *It lowers its significance in that it can be replaced or it's interchangeable with the amidinophenyl final substituent....*

[f. Zhu and Scarborough]

(Zhu, B. and R. Scarborough, "Factor Xa Inhibitors: Recent Advances in Anticoagulant Agents" (2000) 35 *Annual Reports in Medicinal Chemistry* 83-102)

Counsel [Turning to] *Zhu 2000....can you identify where in this article there is references to the Lilly compounds that Dr. Young says are so significantly highlighted here?*

Dr Edwards: ...[T]*hey appear to be buried within the article, the review.*

Counsel: *My understanding is that they are at page 94....[C]an you identify a methoxyphenyl substituent in any of those compounds?*

Dr Edwards: [In]*...compound 64....*[and] *in principle...68a and b....*

Counsel: ...[I]*f you...look at the last full sentence above [the]...table, it says: 'For example, non-benzamidine inhibitor...' and it talks about 69a and see clog D "has a K_i of 10 nanomolar and it doubled the prothrombin time at concentration.' Can you explain that sentence?*

Dr Edwards: ....[T]*hat suggests that it's doubling the prothrombin time, so presumably in this biologically relevant assay it's producing an*

effect that is desired.

Counsel: *And does it identify what's producing that effect? ....[I]s there any data in the narrative, in the text of that article that refers to the significance of the methoxyphenyl substituent?*

Dr Edwards: *....No, I can't see anything in that paragraph that indicates methoxyphenyl is providing some step change or is important for activity.*

Counsel: *...And the compounds that you identified that had a methoxyphenyl substituent, do they have a similar core to the core of apixaban, a bicyclic core?*

Dr Edwards: *No.*

[g. Maignan and Mikol]

(Maignan, S. and V. Mikol, "The Use of 3D Structural Data in the Design of Specific Factor Xa Inhibitors" (2001) 1 *Current Topics in Medicinal Chemistry* 2003 161-174)

Counsel: *This is an article of Maignan and Mikol....Can you give an overview of what this article is about?*

Dr Edwards: *So, it's look thing* [*sic* – looking?] *at 3D structural data...*[in the context of] *the design of specific factor Xa inhibitors. So, it lists on the next few pages a series of differing groups. So, presumably with the literature references, these are groupings that have been found to be disclosed in the literature. So, we have P_1 groups, the central scaffold and P_4 groups. And then there's a discussion on the various binding pockets and how disclosed inhibitors may bind.*

Counsel: *And I think at the first page of that review it confirms what you've already confirmed as being CGK which is about the S_1 and S_4 the pocket and their features, isn't that right?*

Dr Edwards: *Yes.*

Counsel: *And they talk about the three fragments. And in the second column...they teach about each inhibitor being divided into the three fragments, the P_1, the S_1 and the linker scaffold....If you go back...there's a table there of drawn out compounds....Is it possible for you to identify the compound that Dr Young relies on for his analysis in that table?...*

Dr Edwards: . *...24 looks like the compound.*

Counsel: *Okay. And the description...is that: 'Lilly scientists discovered a neutral PI group, the methoxy-benzoyl...'. And it lists the three compounds you've just discussed. '...by screening a combinatorial library based on a diaminophenol scaffold. It showed 17-fold lower inhibition potency than the benzamidine equivalent. A chlorophenyl could also replace the methoxyphenyl with a 6-fold improvement in potency and about the same in vivo efficacy...'. Can you address that section of the review article, please?*

Dr Edwards: ...[I]*t's showing activity with a benzamidine equivalent and then the chlorophenyl analogue could also replace the methoxyphenyl to improve potency by about 6-fold with about the same in vivo efficacy by IV administration. And the benzamidine equivalent compound. So, it looks like they've generated some SAR and replaced the methoxyphenyl with a 4-chloro analogue.*

Counsel: ...[W]*hat does that tell you about the significance of 4-methoxyphenyl as a substituent that's suitable to bind in the S_1 pocket?*

Dr Edwards: *That it can, but it's not necessarily a particularly interesting analogue, because you can replace it easily and improve*

properties within other groupings that are substituted.

Counsel: *...[C]ompound 24 is example 2 that Dr. Young relies on for his analysis....Have you seen that compound specifically identified in any other article or review that you've seen?*

Dr Edwards: *I don't think so....*

[h. Rai – II]

(Rai, R. *et alia*, "Perspectives on Factor Xa Inhibition" (2001) 8 *Current Medicinal Chemistry* 101-119)

Counsel: [turning to the Rai article]....*I'd ask you just to look at the introductory paragraph...:*

> *'Factor Xa is involved in the process of blood coagulation and has emerged as an important therapeutic target in the search for an ideal anticoagulant. Accordingly, there has been an explosion in the number of patents, publications and reviews that have appeared disclosing potent and selective factor Xa inhibitors. This article outlines structural similarities and differences of factor Xa as compared to critical anti-targets: thrombin, trypsin and plasmin.'*

....[D]*o you have any general comments you'd like to make on the article?*

Dr Edwards: *It provides a detailed review of the background and the biology, then some factor Xa crystallisation or crystallography studies against related serine proteases. It indicates how compounds may bind. So, it's a very general review. It talks about DX9054A as a starting compound.*

Counsel: [quotes a later paragraph of the Rai article, *viz.*:]

> *'Trypsin-like enzymes are involved in numerous physiological processes in the body. Specifically, many of the enzymes involved in thrombosis and fibrinolysis are trypsin-like. For a putative drug to have a favorable pharmacological profile, selectivity against anti-targets is critical. Several reasons for endeavoring to achieve thrombin selectivity have been outlined earlier. Plasmin mediates fibrinolysis, the process of blood clot dissolution, and therefore a potential anticoagulant should be selective against plasmin. Selectivity against trypsin is important for favorable pharmacokinetics due to the high concentration of trypsin in the gut.'*

Does that reflect your understanding of the role of selectivity?

Dr Edwards: *Yes....*

Counsel: [quotes a later paragraph of the Rai article, *viz.*:]

> *'Among factor Xa inhibitors, as in the thrombin field, the need to replace amidino groups with less basic P_1 elements has been recognized' – I think that's CGK – '[n]umerous potent and selective compounds have*

been published in the patent literature which contain derivatives of pyridines.'

And there compound 15 is identified...?

Dr Edwards: *Yes....*

Counsel: *Can you identify where in that compound the pyridine is to be found?* [Dr Edwards does so.] *.... It's the six-membered ring with the nitrogen in the bottom?*

Dr Edwards: *Yes, which contain derivatives of pyridine. So, that's identifying example 15.*

Counsel: *And then example 16 next to it?*

Dr Edwards: ...[T]*hat has the four pyrido substituent in both compounds. So, that's the extreme left ring in both cases.*

Counsel: *And that's the one that's binding into the S_1 pocket...?*

Dr Edwards: *If that's what they say.*

Counsel: *...And then going on to compound 17, the isoquinoline is identified as the substituent....*[T]*he isoquinoline is number 17?*

Dr Edwards: *Yes, and 18. So, that would be the ring, the two rings attached together on the extreme left.*

Counsel: ...[S]*o isoquinoline is a bicyclic..?*

Dr Edwards: *Yes.*

Counsel: *So, that's suitable to bind into the S_1 pocket as well..?*

Dr Edwards: *Yes....*

Counsel: *Then coming to number 18 [in fact, 19], this is identified as a thioamidine?....*

Dr Edwards: *It's carbon double bond sulphur.*

Counsel: *And then in number 20 you've got the substituted benzene..?*

Dr Edwards: *Yes.*

Counsel: *....So, it looks like it's the benzene that's lodging in the S_1 pocket, is that what that looks like?*

Dr Edwards: [R]*eally they're better described as phenyl rings rather than benzene, but yes.*

Counsel: *And is there a methoxyphenyl group in any of those compounds?*

Dr Edwards: *Compound 20 has one on the extreme right. And compound 19 does in a similar position, extreme right.*

Counsel: *So, is the extreme right to be understood to be the S_1 pocket or what's your understanding..?*

Dr Edwards: *...[I]t's difficult to be precise just by reading only this paragraph, because S_1 and S_4 can be interchangeable....So...[the] methoxyphenyl rings on the extreme left could bind into S_1 or S_4. And it's not clear to me, just reading this paragraph, that they have any kind of X-ray data to support those findings. If it's a model, a model can be wrong.*

Counsel: *...[D]oes this table include the example 2 that Dr. Young identifies in his report?*

Dr Edwards: *No....*

[i. Summary of Evidence re. 4-methoxyphenyl and S_1 substituent]

Counsel: *...I think in your second witness statement you go through some of the articles and you conclude at paragraphs 1.24 and 1.49 that you*

don't think that there's anything special about the 4-methoxyphenyl group and the S_1 substituent and you conclude that Maignan, the only article that cites it, highlights better replacements; is that a summary of your evidence?

Dr Edwards: *Yes....*

[j. The Appendix to Dr Edwards's Second Witness Statement]

Counsel: ...[C]*an you explain this appendix [to Dr Edwards' second witness statement] please?*

Dr Edwards: ...[T]*his was an attempt to highlight a number of compounds where small structural changes can have an impact on...potency and selectivity and to give some indication of how significant, or otherwise, that structural change is on those parameters....*

[3. Apixaban core a cyclised (rigidified) version of core of DPC423]

Counsel: *...The third justification...*[that Dr Young] *uses for his conclusion that this patent is plausible and valid is that:*

> *'The core of apixaban is a cyclised (or rigidified) version of the core of DPC423. The skilled person would recognise that this modification was likely to increase affinity and/or improve metabolic stability towards hydrolase enzymes. As I describe above, DPC423 had attracted particular attention as an effective, weakly basic factor Xa inhibitor. The skilled person would recognise the similarities between the structure of apixaban and that of DPC423 (which was from the same research group) and the modifications that had been made to it.'*

You address this in your...second witness statement, at approximately paragraph 1.51. I think there's no dispute that DPC423 would have been a known compound at the priority date, isn't that right?

Dr Edwards: *Yes....*

Counsel: *And in...your witness statement you go through different reasons that you see to differentiate between the two compounds* [apixaban and DPC423]. *So, perhaps you could discuss what you see as the essential differences..*[?]

Dr Edwards: ...[I]*f we take DPC423 to start with...if we can go to the bottom ring, we see a methyl amino fragment, so a CH_2 and then NH_2 right at the bottom. That is replaced by the 4-methoxyphenyl group that we've seen already in compound 18.*

Counsel: ...[T]*hey're fundamentally different, are they?*

Dr Edwards: *They are in electronics, sterics, where the groups are positioned, the ability to form hydrogen bond donors, not just acceptors. The density [of] the aromatic ring will be impacted because there's resonance electronation. From the oxygen you can feed the electrons from the lone pair into the aromatic ring, making it more electron rich, which will definitely impact its ability to interact with amino acid side chains in the [S_1] pocket [of Factor Xa]....*

Counsel: ...[W]*hat other significant differences do you identify between the two?*

Dr Edwards: ...[A]*gain on the left structure DPC, if you move up there's a five-membered ring with two nitrogens in and coming off that on the left, there's a CF_3 group in DPC and the primary carboxamide in compound 18....So, in the right-hand structure will be carbonyl to oxygen, then NH_2. So, they're very different groups. The CF_3 is lipophilic, the carboxamide is polar, could be used to form hydrogen bonding interactions, donor site acceptors with backbone amino acids. It's larger. So they're very different groups. But in a carboxamide there you might expect that to alternate lipophilicity and bring it down, whereas the CF_3 group would increase lipophilicity....*

[Asked by counsel at this juncture to explain the terms 'lipophilicity' and 'polarity', Dr Edwards indicated as follows:

> "*Lipophilicity is how water-loving or water-hating a compound is. So, typically, although not always, the lipophilicity may be tested by dissolving the compound in an organic solvent and water and looking at the concentration in both and seeing how well the compound likes to be in a lipophilic solvent versus water. So, compounds which are more lipophilic tend to like the organic phase more and those that are more polar tend to like water more*"].

Counsel: [A]*re there other significant differences between the two compounds that you would like to identify?*

Dr Edwards: *DPC, again on the left-hand side you have the five-membered ring and then coming off to the right is the amide, so the carbon to oxygen double bond and then NH. And that is cyclised in the right-hand structure....*

[Asked by counsel for Teva at this juncture to explain the term 'cyclised', the following exchange took place between Dr Edwards and counsel:

> Dr Edwards: ...[T]*hat means putting it into a ring. So, just like we had yesterday the amide and then the lactam is the cyclic version. Here, you've got an amide in the left structure which is cyclised into effectively a lactam in the right structure.*
>
> Counsel: *....It's kind of more linear, is it, if it's not cyclised, it's not put into a ring, is that correct?*
>
> Dr Edwards: *It's certainly open chained. The exact bioactive confirmation or confirmation in solvent doesn't necessarily mean it's plainer* [sic-planar?]. *It could be at an angle, it's rotating.*
>
> Counsel: *But open is what you say?*
>
> Dr Edwards: *Yes.*

Counsel:	*It's not closed as in a cyclic structure?*
Dr Edwards:	*Yes. Whereas in the right-hand structure, the ring is far closer to plainer.* [sic- planar?]]

Counsel: [A]*re there any other differences between the two compounds that you can identify?*

Dr Edwards: ...[A]*gain, on the structure on the left, the DPC423, if we're moving now past the amide to the right you've got the first six-membered ring, which in the 2 position has fluorine and that is missing in the right-hand structure. So, again...small changes could affect the potency selectivity. Then, at the terminal ring on the left we have* SO_2M_e*. And then on the right we have the lactam substituents. So, they are, again, very different in terms of electronics. You have a different placement of acceptor atoms in the left-hand structure, so they could make different interactions. The lactam on the right presumably is a little bit smaller overall, so it may or may not avoid steric clashes.*

Counsel: ...[S]*o there's no lactam, is there not, in the DPC423 structure?*

Dr Edwards: *Correct....There's an amide but no lactam.*

Counsel: *You mentioned...ridigification of the core. Can you explain that by reference to these two compounds and what it means and what it signifies?*

Dr Edwards: ...[I]*t's an attempt usually to improve a property potency or selectivity. And it certainly works as a strategy, it's a well-known strategy. What is often not talked about...as much are the number of failures en route to the one compound or one cyclic structure that is working. So, with the L configuration the groupings that end in* S_1 *and* S_4 *need to be in optimal positions to optimise their binding. There are many different cores you could construct that might model those groups to be in the right sort of area, but it's very...difficult to predict a priori exactly where they'll be. You don't know how much the protein will flex, for example. So, as a strategy, it certainly isn't something that one core would be made and suddenly an improvement would be seen. Potentially, many cores would be tried. And for various reasons to do with properties and potency, other cores might be dismissed. So, there is significant effort to get the strategy to work, but it certainly can work....*[I]*t's not possible with any certainty to predict the binding mode until you have an X-ray structure.*

Counsel: ...[C]*an you know from looking from one structure to the other that the apixaban on the right is a rigidification of the core in DPC423?*

Dr Edwards: *Yes....*

Counsel: ...[A]*re they both bicyclic cores?*

Dr Edwards: ...[T]*he one on the right is. The one on the left is a mono cycle, if we're looking at the pyrazole ring.*

Counsel: *So, if you look again at what is said by Dr. Young, he said that the core of apixaban is a cyclised version of the core of DPC and he said you'd recognise the similarities between the two structures. What's your view of that statement?*

Dr Edwards: *There's some overarching similarities. You can pick out points of overlap, such as the pyrazole ring itself and an amide and from that an aromatic ring coming off. But there are six structural changes overall, so there is significant difference between the*

structures also.

Counsel: *And...in your evidence yesterday, you mentioned...that...you may be able to predict certain small changes, such as if you'd a methyl, an ethyl and a butyl group and you wanted to add a propyl analogue, you're just extending the chain by one carbon atom, you said, and you might be able to make some predictions based on that. But you did contrast that, I think, with the effect of cyclising or rigidifying the core?*

Dr Edwards: *Yeah....Here, with so many changes, you wouldn't be able to predict at all what the exact potency would be or guess with any accuracy what it might be....*

[4. Lactam]

Counsel: *The next reason that Dr. Young relies on for his view as to the validity of the patent...concerns the introduction of the lactam. He says...that the skilled person would know that the S_4 binding pocket allowed for considerable variability and that, having been presented with it, would consider it plausible that the lactam substituent of apixaban would bind in the S_4 pocket and that you'd recognise that as a skilled person....[I]s there a reason given in the application, the patent application, to support the view that a skilled person would know that the lactam would go in the S_4 pocket?*

Dr Edwards: *No. The lactam as a substituent is a common fragment in drug discovery, there's nothing unusual about it. It may be called to mind by any medicinal chemist as a potential substituent. But you wouldn't be able to predict it would bind to S_4 just by drawing it out on a piece of paper....*

Counsel: *Are there any other substituents that could've gone into the S_4 pocket?*

Dr Edwards: *Many....It's a more forgiving pocket in terms of what it tolerates than S_1. So, there are many, many other groups that could've gone in. In fact 4-methoxyphenyl, for example, is one group I believe has bound to S_4.*

Counsel: ...[I]*f you were looking at a thrombin inhibitor, are there limits to the places a lactam substituent could potentially go?*

Dr Edwards: *I'm not sure it would be hugely different....*[I]*n principle...the lactam substituent could bind in S_1 or S_4 particularly in thrombin, yes....*

[5. Re-use of P1 and P4 groups, carboxamide substituent, and core of apixaban]

Counsel: *Moving on...to the fifth reason relied upon by Dr. Young....*[h]*e says..:*

> *'The P_1 and the P_4 groups, the carboxamide substituent and the core of apixaban are reused many times in Application. Indeed, 32 of the compounds exemplified in the application only have a single point… change from apixaban. The skilled person would understand that this is because the inventors had achieved good results.'*

So, he's saying that you would understand they'd achieved good

results from knowing that and were trying to optimised [*sic* – optimise?] *properties by variations at other positions. What is your view of that evidence..?*

Dr Edwards: ...[I]*t's fanciful, in that you could not know that the team has achieved good results, because there's no data potency selectivity ascribed to any of the compounds in the patent, nor an indication of whether it's a specific or dual inhibitor for factor Xa or thrombin....[B]ecause a group is found multiple times in a patent doesn't necessarily imply that the compound is of interest. Because we don't know what compounds were left out of the patent, in terms of their frequency. And it's purely guesswork to find groups that may be of interest or compounds that may be of interest. But without data, you could not know.*

Counsel: [quotes from Dr Edwards's witness statement where he states:]

> *'While he* [Dr Young] *does not explain his method for preparing this analysis, it appears that he has converted the names of compounds into structures, discarded certain of the structures which appear to differ from the rest, and then performed a counting exercise to identify the number of times a particular substituent is used. This would have been an enormous amount of work....As no data are provided for any of the individual compounds, it is no better than guesswork to conduct this review.'*

That is your evidence...Dr Edwards, is it?

Dr Edwards: *Yes....*[a]*nd if I may add, it is an enormous amount of work and it's prone to error, because it's a human exercise to extract this data, at least at the timeframe that we're considering. And as we've seen with the corrections, it's prone to error. And that's a natural human thing, because we all make mistakes, particularly in a complex operation such as this. So, I'm not sure how much I could rely on data anyway, the numerical values, because of the errors introduced. And I think it's important to put this into the context of what someone in a drug discovery team, as an interested person, presumably working in another company, would view with a patent such as 652 coming out. As has been said before, it was a busy area. Nearly every company, or every company in the industry were working on factor Xa inhibitors. So there would be a flurry of patents and papers and conference proceedings coming out weekly and monthly. And the team member may have an alert on their desktop, either through the company or setting up their own alert system, and they may find many patents coming through. And the value that they would ascribe to those patents, in part, is related to whether they find useful SAR in there. And useful SAR arises from the structures and data ascribed to the compounds. So, it's my view that a team member in another company, if this patent were to come across their desk the day it publishes, would lower their expectations and see less value in the patent because there's no data ascribed to the compound. That makes it a big leap of faith, a guess, as to what SAR may be real and important. So, I think the frequency analysis is something that may not have been performed by everyone, certainly on this patent, because of the relatively low value ascribed to a patent with no data.*

Counsel: *...I might ask you just to look at the actual figure that Dr. Young produced...figure 17....*[a]*nd I would just ask you to look at the actual breakdown and perhaps explain what you see in the figures that are ascribed to the different substituents here.*

Dr Edwards: *...Dr. Young presumably has partitioned the structure into various regions and he's looked for how many different groups in each of those regions appear. So, for example, and for no other reason than it's just in my eyeshot, the P_4 proximal ring, 73 out of 74 have the phenyl ring. So, there's one compound missing from that list and it's substituted or is a different ring differently[sic – entirely?]. You can see the central core, they're all listed as that structure. And I guess the intent here is to say that the higher the frequency, the more important the compound. So, the fact that there's a cyclised core would tell you, according to this analysis, that this is an important substructure within the compound. If you look at R3, for example, the highest frequency group is the CF_3, not the primary carboxamide.*

Counsel: ...[W]*hich of those is in fact in apixaban, can you tell me..?*

Dr Edwards: *13 of 74, the top line.*

Counsel: *So, not the most frequent substituent in that position?*

Dr Edwards: *Not the most frequent substituent.*

Counsel: ...[I]*n terms of the frequency analysis that's been conducted here...it...encapsulates...is it 74 compounds?*

Dr Edwards: *Yes.*

Counsel: *Do you know how those 74 were selected*[?]...

Dr Edwards: *No. I mean, I guess there's 41 compounds missing. What if 41 of 74 were a different group? We're not told that. It could be 41 different groups or somewhere in between. But we don't know anything about the other groupings....Dr Young relies on the frequency analysis in his analysis of WO131 to indicate, I think...*[there] *was six out of however many appearances* [of]*...primary carboxamide...in that patent, therefore, in principle, it's of no interest, because it's a low number compared to CF_3. Whereas here, using the same argument, the most frequent grouping would be the CF_3, that would be the most important. So, if I did not have knowledge of compound 18 at the time and I performed this frequency analysis and revealed the same figures as we see here, I would naturally...be interested more in the CF_3 compound. That is where I would say the more interesting compounds in this patent are....*

[6. Greater Scale of Synthesis]

Counsel: *The final reason that Dr. Young relies upon relates to Example 18, which you just mentioned[, is]...that it was synthesised in a bigger scale than other compounds of the invention....And he talks about there being a second recrystallisation, I think, in this step [F] of the synthesis and he also focuses on the amount that was crystallised. And you might just perhaps navigate us through that part...of the synthesis description...and explain your view in respect of it.*

Dr Edwards: *Yes, so I guess they are taking the ester for part B and converting that to the primary carboxamide in a sealed tube, which is an often used way of preparing compounds in the research laboratory. But it's completely unsuitable to development and scaling up, because*

it's a sealed tube, under pressure, so it could be a very dangerous reaction - which speaks to what I said earlier, that what matters is making the compound, not how you do it. Then they add water and precipitate the solid, which they collect. And that's purified by silica gel. And that affords 3.5g of a white solid, which presumably is an amorphous solid, it's not crystalline....So, a portion of this was recrystallised....So, they crystallise from DCM, dibromoethane ethyl acetate, and they get two and a half grammes of title compound. So, it's not clear what the yield of that is, because they say 'a portion of the solid', so I don't know how much of the three and a half grammes was actually used - presumably at least two and a half grammes. The remaining solid and filtrate material were recrystallised from isopropyl alcohol, so presumably the solid and the filtrate material - so, that is the dibromoethane ethyl acetate - is evaporated down, again giving an amorphous solid, not a crystalline material. That's combined with the remaining solid from three and a half grammes that wasn't used, I assume, and this was crystallised from isopropyl alcohol. And this gives an additional 05.7g, to give a paper total of 3.07g. So, what's not clear to me is the purities of these two batches of compound. It is never the case that you would combine batches of material separately without knowing that it's the right compound, the right structure and the purity and you're satisfied within whatever limits you have in the project that the purity is good enough to combine. And we don't know what that is. Particularly if you're going to more advanced studies, whatever that means, such as using animals, ethically you wouldn't want to put in a compound which is impure. And that certainly wouldn't have been the case with BMS; they would've thought very carefully about what animal experiments they use. So, it's certainly not clear to me which batch has what level of purity and whether it was combined. It could be that the first crystallisation to give the two and a half grammes provided an impure batch and they decided to get a second batch using a different solvent. So, it could be that the 0.57g is actually the pure material that was taken forward, it's just not known. It gives a total of 3.07g. This is a very modest amount of material. And I'll justify that as follows. If you were to walk into a medicinal chemistry laboratory and open the drawers of any chemist's stash of glassware that they use typically on a day by day basis, for example, you would see a round-bottomed flask....[a]nd a typical scale that a medicinal chemist may work on is anywhere between a one ml volume and a two litre volume, depending on exactly what they're asked to do. So, that is a typical scale that medicinal chemistry work on. Much on [*sic* – more?] *than that, you're potentially risking safety by having runaway reactions, bigger reactions, you don't have a fume hood that's big enough to encompass the glassware. So, that tends to be done elsewhere. So, it's perfectly normal to synthesise gramme quantities of compounds. And that can include final compounds. So, 3.07g, if that were the total pure batch that were taken on, is not a significant amount of material, it is a perfectly normal range of material that is prepared. It doesn't necessarily mean that that 3.07g was taken forward. The utility of that may be for other things than simply it is an interesting compound and we're taking that further forward through all of the discovery assays. It could be*

used as a tool, for example, to validate the rabbits shunt model. Particularly, as I would argue, this is an early stage patent....So, if it's early it's also possible that the internal rabbit AV shunt model that they're developing needs compounds to validate it. And in a real world, a project doesn't exist in isolation, it exists in the pressure and the cauldron of other projects ongoing within the company....So, if this is an early project at this stage, it's perfectly possible that some of this material was diverted to validate the AV shunt model and not to go any further. So, we don't know from the quantity of material synthesised where that ended up, which assays it ended up. But the quantity is not unusual.

Counsel: *And do you necessarily know that it was used for the factor Xa inhibition?*

Dr Edwards: *I guess not. Because there's no data in the patent on that.*

Counsel: *And in terms of the data that is there, there is an NMR figure which we've looked at before. But you've identified to us different characterisations that can appear in examples.*

Dr Edwards: ...[T]*o me, if a company cared about a compound, it would characterise and purify and identify, with data, that this compound is cared for. And we've seen other compounds with high res mass spec identifying the molecular formula. There doesn't appear to be any of that data here, it's a simple proton NMR spectrum, which is often what's obtained just to give an indication that you've got the right structure. You're looking for the addition of, in this case, the lactam CH_2 groups, for example, and seeing you can integrate for the right number of protons, 'Okay, we've got this grouping in, the reaction has worked'. But there's not a lot of data to characterise the compound.*

Counsel: *...I think in your witness statement...you call it guesswork by Dr Young to attach significance to the amount synthesised. Is that your evidence?*

Dr Edwards: *Yes.*

Counsel: *And you also discuss in your witness statement intermediates....*

Dr Edwards: ...[T]*he scale of the reaction could be due to diverting an intermediate to make multiple compounds. So, it's perfectly possible that the ester at step E, and even before – before it's coupled to the terminal ring, I believe there is an iodine substituent which is reactive for various carbon/carbon bond coupling reactions. So it is perfectly possible you make, at scale, an intermediate that you then apportion out into a number of reactions. If you had ten different monomer inputs for the carbon/carbon bond formation and then different amines, instead of giving the primary carboximide you give derivatives, that's potentially 100 compounds you can make. You need enough to screen each compound, so you would work at a greater scale. So, I can see en route to compound 18 intermediates that could be diverted to library chemistry. And so that's a reason that the compound was initiated on a large-scale. It could be that the team were unsure of the yields. They're not super. But that is perfectly normal; as I say, for discovery chemistry they don't have to be perfect. Perhaps the chemist making compound 18 was unsure that the reaction would be successful and so what they did was increase the scale and they were fortunate enough to get more than they had anticipated and that's why they have the material that they have.*

Counsel: ...[I]*f you...look at what's in the last part of the synthesis of*

	Example 18, is there a scientific reason given there to have a view about the effectiveness of a factor Xa inhibitor?
Dr Edwards:	*In the experimental on p.222? No, there's no indication or relation to factor Xa in these paragraphs.*

15. Prior Art

1017. Counsel for Teva turned next to the issue of prior art, noting that Dr Edwards concludes in his report that there is "*a very high degree of similarity*" between WO131 "*which is the prior art*" and WO652 "*and there's no information as to whether any of the compounds are particularly potent or selective here*". She then asked whether, in Dr Edwards's opinion, there is "*any relevant contrast between the information disclosed in WO131 and 652*". To this, Dr Edwards responded "*Not greatly, no. They're very similar.*" Asked next whether he perceived there to be "*any difference in the data disclosed in the two sets of compounds, or two sets of patent applications*", Dr Edwards responded "*Not that I perceive, no. They're similar.*"

16. The Lipinski Rules

1018. Counsel for Teva noted that Dr. Young raises an issue about the Lipinski rules in the course of his witness statements and effectively invited Dr Edwards to make comment in this regard. Dr Edwards responded:

> "*I worked with Chris Lipinski whilst at Pfizer and sat in meetings with him and had internal-only discussions as to the background to this and why it's important. And Chris's view always was that chemists vastly overinterpreted the rules, the guidelines. He never intended that they would stop a company or a chemist making a compound, it was merely an alert in the Groton database to say 'Please note it breaks one or two of the guidelines'. So, there's an overreliance. And the rules are more appropriately applied to the early stages – library chemistry, hydropic screening. And that comes out from Chris's 1997 paper. They're not generally applied and only in retrospect to the lead optimisation phase, the later stages of drug discovery.*"

C. Cross-Examination

1. The Lipinski Rules

1019. Counsel for BMS brought Dr Edwards briefly to the Lipinski Rules, returning again to it later. He referred to the fact that the Lipinski paper was published just before Dr Edwards joined Pfizer, that he (Dr Edwards) had pointed out in his evidence that it was used as a guide within Pfizer to keep weights below 450 (to which Dr Edwards indicated that "*In our group, it was. Different groups, different sites had different interpretations of those guidelines and used them differently*"). He then asked about the answer that Dr Edwards had given regarding the Lipinski rules while under examination, at which point the following exchange occurred between counsel and Dr Richards:

Counsel:	[T]*he information you gave the court about communications from Dr. Lipinski to you in private meetings are not something that is private knowledge until* [you]*...mention*[ed] *it...just now?*
Dr Edwards:	*The fact that Chris believed that the industry overinterpreted the guidelines is public knowledge....*
Counsel:	*It's not anywhere in the papers in court, is it?*
Dr Edwards:	*No, but it's been discussed in conferences in open discussions.*
Counsel:	*And when you say – when he says overinterpreted, they are guidelines, aren't they?*
Dr Edwards:	*They are...*

2. Substance of Dr Edwards's Criticisms

1020. Counsel suggested to Dr Edwards that "*you've been very critical of the 652 application and what it contains*", it being suggested by counsel that Dr Edwards's evidence in chief was "*essentially to this effect*":

> "[t]*hat if a document is published about a molecule that doesn't characterise it in full, support it by both potency selectivity and biological data, bioavailability and the like, that you would regard the publication in relation to that as being of relatively little scientific value and as indicating that the company doesn't really care about the molecule*".

1021. To this, Dr Edwards responded as follows:

> "*The primary determinant there is primary potency, in this case in factor Xa. So, that is what I would base my opinion on, not necessarily bioavailability or metabolic stability or any of the other associated data that you may generate in a compound. But for an initially disclosing patent not to disclose data for any of the compounds related to primary potency, that would reduce my level of interest in the patent.*"

1022. Counsel then put it to Dr Edwards that "*it was common at this point in time, at the turn of the century, for patent applications to be filed with no data...*[Y]*ou know that was commonly done, don't you?*" To this, Dr Edwards responded that "*It was done. I wouldn't know whether it was common, whether there was a preponderance for no-data patents versus data patents. I couldn't comment on that. But it certainly was done.*" Respectfully, I do not see in this exchange that BMS, as Teva puts matters in its closing written submissions, was "*making some case that the requirements of validity can vary according to some asserted pattern of patent prosecution strategies from time to time*".

3. The Drug Discovery and Drug Development Process

i. General

1023. Counsel touched upon paras.6.28-6.29 of Dr Edwards's written statement. They appear under the heading "*General Points on the Drug Discovery Process*" and state as follows:

> "*6.28* *Drug discovery is an expensive and time-consuming undertaking. It typically occurs as a staged process in which the Skilled Team is initially looking for compounds that act as a starting point (having some degree of activity against the target) through to optimising and refining the chemical structure of a compound, which may become a clinical candidate.*
>
> *6.29* *The process is generally iterative. The medicinal chemist will synthesise a series of compounds and, with the skilled pharmacologist, examine and analyse their characteristics, including potency and selectivity. More promising drugs advance from initial in vitro assays to testing in animal models and eventually humans*."

1024. Focusing on the drug discovery and development process, counsel put it to Dr Edwards that the starting point, the first step, is to look at work that has already been done in the area, *i.e.* the literature search. Dr Edwards confirmed that this was so.

1025. Counsel noted that Dr Edwards has described the drug discovery and development process as iterative, by which he understood Dr Edwards to mean that "*you design, synthesise, test and then, using the information from that work, identify further compounds to synthesise and test*". Dr Edwards confirmed that this was so.

1026. Counsel then put to Dr Edwards that when trying to identify potential inhibitors of particular biological pathways, "*you're looking initially for potency against the chosen target molecule*". Dr Edwards confirmed that this was so.

1027. Counsel also suggested to Dr Edwards that selectivity would be an issue "*in the sense that you'd bind with the target, but very preferentially and as close as possible to binding to nothing else which might affect other biological activity*". Dr Edwards agreed that this was so, and further agreed when it was put to him that "[s]*ide effects of drugs may result from less than perfect selectivity*".

1028. By way of summary, counsel suggested that "*the process involves going around a development loop, each circuit of which follows from the synthesis and testing work done in the previous iteration*". Dr Edwards agreed that this was so for the discovery section. Counsel suggested further that "[p]*otency and selectivity are, of course, only the primary essential characteristics of an effective inhibitor*", with which Dr Edwards also agreed.

ii. Oral bioavailability

1029. Turning next to the issue of oral bioavailability, the following exchange transpired between counsel for BMS and Dr Edwards:

Counsel:	*The drug also has to be administered effectively* in vivo..?
Dr Edwards:	*Yes.*
Counsel:	*And generally, oral administration is preferred to intravenous, particularly where a drug is to be used by patients in their normal environment rather than in a hospital setting?*
Dr Edwards:	....[T]*hat depends on the particular disease state.... But in general, yes.*
Counsel:	*....If I put it more generally; non-invasive administration is preferable to invasive administration?*
Dr Edwards:	*Yes.*
Counsel:	...[N]*ormally drugs are taken orally, aren't they?*
Dr Edwards:	*Normally. But it is culture specific....But in general, yes.*
Counsel:	*And to be taken orally and to be effective, it has to be capable of surviving passage through the digestive tract and being absorbed into the bloodstream?*
Dr Edwards:	*Yes....*
Counsel:	*The preferred route is to design the drug so that it will pass from the gastrointestinal tract?*
Dr Edwards:	*Yes....*[But] *it can be the case that if the market is so important, a company would invest effort in fixing broken properties, if you will, because they're not optimal for...simple oral delivery....*
Counsel:	*Generally speaking, it would be fair to say...that oral bioavailability is a key property of an effective therapeutic agent?*
Dr Edwards:	*Yes....*
Counsel:	*You would agree that the absorption, distribution, metabolism and excretion properties of a molecule need to be tested and determined?*
Dr Edwards:	*Yes.*
Counsel:	[T]*hen if they are unsuitable, you can try and optimise the molecule, optimise its structure in order to give the drug a suitable pharmacokinetic profile?*
Dr Edwards:	*Yes....*
Counsel:	*If your results indicate that you're close to something acceptable, something workable, small changes are likely to follow; if you*

seem to be way off the target, you may try again with a different approach?

Dr Edwards: *Yes.*

Counsel: *At each stage, the molecule has to be tested to see how it behaves.*

Dr Edwards: *Yes.*

Counsel: *And if you are in the process of making small changes to a molecule which looks promising, you have to test each change to see how it's affected the behaviour?*

Dr Edwards: *Yes....*

Counsel: *Dr. Wargin suggested that substantial oral bioavailability would be desirable. He gives 70% as a figure. I think it would be fair to say that significant numbers of drugs have poorer oral bioavailability than that, don't they?*

Dr Edwards: *Yes.*

Counsel: *But you would like as much as you can achieve, would that be fair?*

Dr Edwards: *Yes.*

Counsel: *He also points out that it is desirable that the molecule has similar effects in a patient over time and across the patient cohort....*[Y]*ou would agree?*

Dr Edwards: *Yes....*

Counsel: *For a drug that is to be taken orally on a continuing basis, the ideal is to have a molecule that has a half life which allows it to be taken, ideally, once a day, or possibly twice a day, while maintaining the dose in the bloodstream between the minimum therapeutic dose and the maximum therapeutic dose?*

Dr Edwards: *Generally yes....but it can be other markers like once a week....*

Counsel: *When you...determine the half life of a drug, you work stepwise and iteratively again...to modify the behaviour of a molecule to a point where it has a combination of properties which make it...effective as an inhibitor and biologically acceptable?*

Dr Edwards: *Yes.*

Counsel: *And...the process can frequently fail?*

Dr Edwards: *Yes....*

Counsel: *It's a long and expensive process, doing this, so one therefore tries to eliminate clearly unsuitable molecules at an early stage..?*

Dr Edwards: *Yes.*

Counsel: *There's no point in going down the development track for an inhibitor with a molecule which has not been shown to have suitable potency and selectivity; you're just wasting your time?*

Dr Edwards: *Generally. Although it's the balance of properties. You can forego some potency if other properties allow you an efficacious drug....*

Counsel: *And if you cannot achieve good oral bioavailability in initial testing, there's no point in going further..?*

Dr Edwards: *No, that alludes to the point I made earlier on with formulation....You can modify....*[a]*nd that's a common strategy and has been done...*

iii. Factor Xa and what was being done at the priority date – I

1030. Counsel put it to Dr Edwards that when it came to Factor Xa inhibition and what was being done at the priority date, it was well known at the priority date of the patent that nanomolar potency was required in order to be able to achieve a therapeutic dose of the drug in the bloodstream. Dr Edwards agreed that this was so.

1031. Counsel also suggested that when it came to Factor Xa inhibition and what was being done at the priority date, molecules which did not show potency in the nanomolar range on initial screening would be eliminated from the programme, subject to being used as a template for making changes to ascertain whether the properties could be improved by doing so. Dr Edwards did not quite agree, volunteering an answer which was then summarised by counsel (in terms that Dr Edwards agreed with), namely that "*a molecule which didn't show sufficient potency might be considered to be worth taking forward because there were aspects of its structure and the knowledge about it which indicated it was capable of improvement*".

1032. Dr Edwards also indicated that by 'taking forward', he meant into the next iterative round of design, synthesise and screen, agreeing when counsel put it to him that "*It's all about compromise and adjustment and achieving a balance of properties that gets you to the target*". When counsel put it to Dr Edwards (as a medicinal chemist) that that knowledge is something that the skilled medicinal chemist would bring to the table when designing a drug development programme for a new small molecule Factor Xa inhibitor, indicated his agreement to this, though adding "*...as would other members of a skilled team as well. A pharmacologist, for example, pharmacokineticists*."

iv. Literature Search

1033. Counsel led Dr Edwards next to paras. 6.39 and 6.40 of his statement, where Dr Edwards states as follows, under the heading "*Factor Xa Inhibitors*":

> "*6.39* *In order to place myself in the position of the skilled medicinal chemist in 2001 joining a factor Xa drug development team in 2001 I carried out a literature search. The skilled medicinal chemist would join a new project team without necessarily specific knowledge of the therapeutic area or target. As a result of this, they would discuss these with other members of the project team, or the Skilled Team as defined above, as well as carry out literature searches to identify publications which may assist with developing this relevant knowledge and understanding.*
>
> *6.40* *Accordingly, l used PubMed as a search tool for my literature searches. PubMed was widely available in 2001 and the skilled medicinal chemist and Skilled Team would have regularly used this database to locate relevant scientific papers. As the skilled medicinal chemist would have been interested in obtaining papers more broadly about factor Xa, whilst still focussing on the aim of developing a small molecule inhibitor, I therefore ran a literature search which initially returned 2,196 results. I ran a further search to narrow down the number of results. With both searches, the date range used was 01/01/1970 to 31/12/2001, in order to capture as many relevant references as possible prior to the end of 2001 date. This second search returned 18 results. From this list, I reviewed each title and identified papers of interest to the skilled medicinal chemist based on the relevance of the title to the development of factor Xa inhibitors.*"

1034. In response to various questions from counsel for BMS, Dr Edwards indicated that (i) he would conduct this kind of literature search, and (ii) such a literature search would assist in developing the medicinal chemist's relevant knowledge, particularly if she was coming from outside the field. In terms of the searches initially done by Dr Edwards there was a disparity between what he told Pinsent Masons (solicitors for Teva) and what he had previously said in court in his evidence. Dr Edwards indicated that he had misremembered the terms that he had used when he was giving his oral evidence and that what he had disclosed to Pinsent Masons was correct.

1035. Counsel for BMS put it to Dr Edwards that in doing such a literature search one is "*presumably principally interested in recent work*", in this case "*shortly before 2001*"; Dr Edwards

answered "*Yes*" to the foregoing. The foregoing being so, counsel queried what was the point of searching back to 1970. To this, Dr Edwards answered as follows:

> "*Simply to capture any possible documents. I have not worked in factor Xa research, so for me this was a fresh area, so it was important to overinterpret where the papers may be lying, as I did not know a priori when the first factor Xa publication arose. So, I chose a date that was far back in time and I knew it would be much further back than in factor Xa research, so it would not pull anything back. So, it was purely to capture as much as I could, not knowing when the first factor Xa paper published.*"

1036. In response to various questions from counsel for BMS, Dr Edwards indicated that he did two searches, the first search returned 2,196 results, the second search returned 18 results, and that he used three search terms 'Factor Xa inhibitor', 'Factor Xa small molecule inhibitor', and 'Factor Xa K_i'. Counsel then asked what happened to the results from the third search, to which Dr Edwards indicated that he believed it was the Factor Xa K_i search, that it likely produced too many hits for him to process.

1037. Of the search that yielded 18 documents, counsel for BMS queried why seven of them were not set out. Dr Edwards responded that they were "less interesting". When asked were they about Factor Xa, Dr Edwards indicated that "*They could've been. But they could've been about hardcore biology aspect sequence-specific points and nothing to do necessarily with structures or whether medicinal chemistry would impact. So, I believe they could've been relevant to factor Xa, just less relevant to a medicinal chemist.*" When counsel for Teva put it to Dr Edwards that four of the results that he *did* list did not actually appear to be about Factor Xa at all (Nos. 2, 3, 5 and 6) and asked if he found them to be of any value, Dr Edwards indicated as follows:

> "[A]*s I explained yesterday, I've spent many years in hit discovery, so working at the very early stage...where we would look at the outputs from a high throughput screen, we would look at working with a biologist to enable target discovery. Because it was an early stage project that I've worked on many times, I know that, looking at allied targets, similar targets brings value in. I took the view, not having worked in factor Xa research previously, that the area was relatively new and was at that hit discovery stage, effectively. It was perhaps moving on a little, but around that stage. So, I believe that looking for papers that were related to factor Xa, such as thrombin, TPA – and the ones I list there generally will have factor Xa mentioned and compounds with data associated with factor Xa, even though the primary point of the paper was a related target – for me, that is still useful, because you get data, positive or negative, for a factor Xa assay that can help construct SAR, because it can tell you, well, against this particular target which you're interested in in factor Xa, this is the kind of structure activity relationship or data you find to increase or decrease activity. That may translate into factor Xa research. So, I believe that is of value.*"

1038. Having ascertained that Dr Edwards had set out between §§6.43 and 6.47 of his witness statement the learning that he extracted from the papers that he found, counsel for BMS queried whether any of that learning had come from any of papers 2, 3, 5 and 6, and if so, which. To this, Dr Edwards responded as follows:

> "*I can't remember in detail every single paper and every single point within it. But it's certainly possible that the points 6.43 to 6.47 don't include those, because the data in those papers are reviews for SAR studies, whereas 6.43 to 6.47 primarily is indicating compounds that may be of interest. So, they're two different approaches. And the search for SAR data is still valid, because if I were a team member, that would be carried on. And I think that goes beyond, a little bit, the search terms that were asked for here, which is to indicate compounds of interest. So, they are still relevant, in my mind.*"

1039. When it was put to Dr Edwards that their relevance had not found its way through to his statement, Dr Edwards accepted that this had not occurred in respect of the most prominent Factor Xa inhibitor compounds.

1040. When counsel for BMS suggested that Dr Edwards had not specifically looked for review articles, Dr Edwards indicated that the search terms had returned the hits that they had returned and he had focused on those.

v. Zhu and Scarborough – I

1041. Counsel turned next to the Zhu and Scarborough article, noting that (i) the abstract sets out what the article is about, (ii) Factor Xa is an attractive biological target, (iii) the article is talking about the work done at Core Therapeutics (where the authors were employed), (iv) by way of summary of the results achieved, the article stated that:

- (a) the results "*demonstrated that small molecule factor Xa inhibitors could be advantageous over Warfarin and LMWH*", *i.e.* they were exploring small organic molecules as reversible inhibitors,
- (b) "*From a medicinal chemistry perspective, significant insight has been gained regarding the in vivo antithrombotic efficacy and pharmacokinetic behaviours of each class of factor Xa inhibitors. This review will focus on the design and discovery of transition state factor Xa inhibitors as potential parenteral anticoagulant agents*", and
- (c) "*Several excellent comprehensive review articles on factor Xa inhibitors have appeared recently*" (and then it goes to references 1-4).

1042. As to (c), counsel for BMS queried whether Dr Edwards had thought to look at the references. The following exchange then occurred between Dr Edwards and counsel for BMS:

Dr Edwards:	...[W]*hen the interested person joins a team or joins the project, review articles are certainly one area of interest, but there are many others. So, I took the view that the papers that I returned would be sufficient to provide an indication of the area without diving further into extracting further references....I made a deliberate attempt to limit obtaining every possible article that there could be.*
Counsel:	*....Are you saying that what you did reflected what you thought the skilled person would have done at the date or did not reflect?*
Dr Edwards:	*Did reflect. Because the learning would've been obtained from other areas - from people, from their reviews, their papers that they would give you. This was an exercise, to me, in someone coming in who has no notion of factor Xa research and looking for pertinent references, which is what I did. In fact, if you were working in a pharmaceutical company, this would not be your only and sole source of information. So, I took the view that you would not find everything in a literature search and you would talk to your colleagues and obtain further information that way.*
Counsel:	*So, on your own evidence, Dr. Edwards, the task you were performing was...artificial, because you didn't have anyone to talk to?*
Dr Edwards:	...[I]*t's not artificial, in that I found pertinent references.*
Counsel:	....[I]*t might be artificial, in that you missed relevant information.*
Dr Edwards:	*I think any search can miss relevant information....whether you find reviews or not....I made the decision to fix my search on what*

I found in the primary literature from the search itself.

Counsel: ...[Y]*ou made a conscious decision not to look at articles which, on their face, might well have been relevant?*

Dr Edwards: *I made a conscious decision not to delve too deeply into the literature.*

Counsel: *You do accept...that the Zhu and Scarborough paper....contains a great deal of relevant information? ...*

Dr Edwards: *I don't know. It contains relevant information....*

Counsel: ...[A]*re you saying you still haven't reviewed it properly?*

Dr Edwards: *I don't have every word memorised, so I cannot say, without studying it right now, whether I perceive it to be a great deal of information or just relevant information.*

vi. Factor Xa and what was being done at the priority date – II

1043. Returning to the work that had been done on Factor Xa at the priority date, counsel elicited Dr Edwards's agreement to the following:

(i) at the priority date, Warfarin was the only oral anticoagulant available;

(ii) its vagaries and weaknesses were well documented and understood and the reasons for them understood;

(iii) he did not dissent from the agreed CGK document in this regard;

(iv) as a result of the deficiencies with Warfarin, it was fair to say that by the priority date there was a substantial clinical need to provide effective oral coagulants to replace Warfarin which had fewer side effects and a larger therapeutic window;

(v) thrombin and factor Xa had been identified as the best potential targets for the therapy;

(vi) thrombin was an initial target and was thought to have potential drawbacks when compared with factor Xa (the reasons for that are set out in the agreed common general knowledge);

(vii) there were two specific reasons why factor Xa was identified as a good target, being (a) it lies at the heart of the coagulation cascade at the point where the intrinsic and extrinsic pathways meet and is, therefore, necessarily involved in coagulation, and (b) it only has antithrombotic effects so it is less complex in its behaviour than thrombin;

(viii) an additional advantage was that Factor Xa catalyses the production of thousands of thrombin molecules and, therefore, by inhibiting factor Xa one can have a much larger effect on the later parts of the coagulation cascade by way of a small dose;

(ix) it was, therefore, no surprise that (as noted at §51 of the agreed CGK document) at the priority date there was a huge amount of work being done across the pharmaceutical industry looking for small molecule factor Xa inhibitors?

vii. Betz

(Betz, Andreas, "Recent Advances in Factor Xa Inhibitors" (2001) 11(6) *Expert Opin. Ther. Patents* 1007-1017)

1044. Counsel turned next to the Betz article (which involves a review of Factor Xa inhibitors). Counsel noted that the article included a list of pharmaceutical industry actors working in the field of research that is at the heart of these proceedings. When Counsel for BMS indicated that several of these actors were not mentioned in Dr Edwards's paper, Dr Edwards indicated that he did not consider that he was required to list all the companies working in the field. Counsel responded that what he was suggesting was merely that the difference between what Dr Betz showed and what Dr

Edwards have found "*might indicate that your search was perhaps less effective than it might have been at locating the work that was being done*". To this Dr Edwards indicated that an alternative was that he chose not to reproduce every single company that was involved in factor Xa research, because he did not consider that to be necessary.

1045. Counsel turned next to consider some of the work reported in the Betz article. In the questions that followed, counsel elicited Dr Edwards's agreement to the following by reference to the article:

(i) low molecular weight inhibitors were favoured;

(ii) extensive empirical studies showed that "*Inhibitors comprising two basic moieties linked by spacers of appropriate length were demonstrated to be most potent*" and immediately picks up DX9065a;

(iii) the I-shaped configuration with the two binding groups on the limbs of the L and the scaffold in between them is a universal factor in the design of these molecules;

(iv) that "[i]*n order to develop drugs with higher bioavailability and half-life than DX9065a, several groups tried to reduce the positive charge of inhibitors*"

(v) recent advances in inhibitor design were able to replace some amidino groups with less basic residues, similar efforts to replace other basic groups were also evident from the patent examples, and the foregoing might yet produce new avenues for the design of more efficient inhibitors with good oral bioavailability, which could provide a viable alternative to heparin.

(vi) it was well known at this time that nanomolar potency was desirable;

(vii) it was clear that researchers understood what they were looking for, from the observation that "*Although the newly generated structures have almost no similarity with natural ligands... the reported Ki values of these compounds for Factor Xa are on average in the nanomolar or even picomolar... The high potency... results potentially from the bidentate structure.*"

(viii) that the work being done, as a result of which the patents were filed, was work aimed at producing that level of potency; (The point being put to Dr Edwards in this regard, though it arose at a point when the Betz paper was touched upon, was not that, despite the absence of data, Betz identified a plausible therapeutic candidate from the patents. The point being put to him was that the work underlying the patents would have resulted from people looking for nM compounds. That is wholly uncontroversial: after all, the whole field was looking for nanomolar compounds).

(ix) that there would be no point in doing the research otherwise, because it is known what is needed;

(x) what was being looked for was molecules which bind to Factor Xa with sufficient potency and selectivity to make them worthwhile candidates to take forward for further evaluation (Dr Edwards described this as a "*reasonable assumption*");

(xi) that he could not point to any indication in the Betz paper which indicated that Betz was reviewing the patents for any purpose other than to set out the compounds which people are researching with a view to the above-described end;

(xii) that one could read the absence of data in a number of the reviewed patent applications as indicating that it was not uncommon around that time to file patent applications without data;

(xiii) that one can, generally, predict, to some extent, how variations are likely to affect the behaviour of the material;

(xiv) that there is no indication in the "*Expert Opinion*" section of the article to suggest that it involved a comprehensive review, irrespective of merit.

viii. Lipinski's Rule of Five

1046. Counsel suggested next that the abstract to Lipinski's article suggests it to be "*about finding ways to estimate solubility and permeability in discovery and development settings and to identify guidelines which will improve absorption or permeation.*" To this, Dr Edwards responded that this was incorrect and that counsel had conflated two areas of research:

> "*One is research, one is development. Development looked for thermodynamic solubility, which is the true solubility of a compound. Lipinski states in his paper he uses turbidimetric, obviously for solubility, which is a quick and dirty method for solubility more akin to the high-through biological assays and looking at the solvents used for assay development and application. So, it's a way of providing a rule of thumb, if you will, and the values will usually be higher in terms of the solubility that they provide for compounds. So, it is only useful, and Lipinski says this in the paper, for early stage research, not for development.*"

1047. Noting that Lipinski's analysis is specifically targeted at medicinal chemists and that he describes the target audience as having very strong patent recognition skills, counsel asked what Dr Lipinksi means by this. To this, Dr Edwards responded that Lipinski means that the target audience are good at deducing structure activity relationships and structure property relationships within series and between series, precisely the sort of thing (Dr Edwards agreed) that a medicinal chemist will do as a matter of routine.

1048. Counsel turned next to consider the substance of the rule of five, the following exchange ensuing between counsel and Dr Edwards, after counsel identified where the 'rule of five' is to be found:

Counsel:	*You would agree that complying with those five – I'll call them rules for the moment... – will significantly increase the possibility that a molecule will have good oral bioavailability and absorption?*
Dr Edwards:	*...If used correctly....*[T]*he paper itself states that the real application of the...rule of five is [to]...early stage discovery....When you have too many compounds you...need a way of reducing those numbers to something that has a higher likelihood against several criteria of being quality hits....It was less...used to design compounds in the lead optimisation phase – ...as you progress through a discovery....But in reality, the medicinal chemist would often calculate the compound's compliance with the rule of five after the compound was made....*[I]*n my experience it wasn't applied to design a compound and eliminate or include a compound in a set to be synthesised at the lead optimisation.... It was more important and more better applied at the earlier stages....*
Counsel:	*It's a good starting point?*
Dr Edwards:	*Yes....*
Counsel:	*I got the impression from* [your report]*...that you thought it was wrong to refer to them as rules....*
Dr Edwards:	[T]*hey are guidelines....Lipinski himself...*[has written that] *it was not meant to deter any chemist from making any compound, it was simply a guidance that 'You are exceeding the rule of five in one, two, three parameters', whatever it might be....*
Counsel:	[I]*t is Lipinski's coinage, 'The rule of 5'....*
Dr Edwards:	*Because that sounds good....a flashy mnemonic to make a splash*

> *in the industry....But...they are guidelines, not rules hard and fast....*[I]*t's a simple way of expressing...a thought experiment on how that was delineated in practice and how it could be potentially useful to chemists at various stages.*

1049. Dr Edwards agreed that the paper was a departure from previous thinking, being the first time anybody had thought about defining the design process and starting with this kind of guide. Counsel then turned to exceptions to the 'rule of five'.

1050. In his succeeding questions about the 'rule of five', counsel elicited the following evidence from Dr Edwards:

(i) the paper talks about the number of drugs which break the rule of five being between 8 and 12%, depending on the parameters applied;
(ii) the goal of the 'rule' is to improve efficiency, improve the starting point and give a direction (Dr Edwards again noting that "it's better applied to the earlier starting phases rather than toward the end);
(iii) application of the 'rule' does not guarantee that a molecule will have useful properties, but it makes it more likely that it will, *i.e.* it stacks the odds in favour of the molecule having oral bioavailability;
(iv) the use of the rule to eliminate candidate molecules at an early stage is a sound approach, "if the terminology of *'candidate'* isn't confused with the drug candidates;
(v) a molecule that conforms to the rule of five is more likely to have useful bioavailability properties than one which does not;
(vi) when a medicinal chemist is presented with a molecule which meets the 'rule of five', the reaction is likely to be more positive than it would be to one which does not;
(vii) the 'rule of five' is derived from the 90th percentile of registered drugs, so there are bound to be exceptions (including among successful drugs); and that this was bound to be the case because of the way the rules were created; and
(viii) the exceptions therefore do not really confirm anything other than that there are exceptions.

(ix) Maignan and Mikol – I

(Maignan, S. and V. Mikol, "The Use of 3D Structural Data in the Design of Specific Factor Xa Inhibitors" (2001) Vol. 1, No. 2 *Current Topics in Medicinal Chemistry* (161-174)

1051. Counsel for BMS turned next to consider the Maignan and Mikol article (and small molecule factor Xa inhibitors), one of the articles that was identified by Dr Edwards in his literature search. Dr Edwards agreed with counsel's proposition that this was a very good article in terms of giving a "*pretty good overview of the state of play at the priority date*".

1052. Counsel noted how the article characterises the active site of factor Xa, explaining that there is an S_1 pocket, which is quite deep, with an S_4 pocket also being described, the learned authors observing that "*Each fXa inhibitor reviewed in this paper can be divided into three fragments: The P_1 group which binds in the S_1 pocket, a linker or a central scaffold designed to project the substituents appropriately into the pockets and the P_4 group which interacts with the S_4 pocket.*" Dr Edwards agreed when it was put to him that the foregoing quote represented a good overall summary.

1053. Dr Edwards subsequently agreed (by reference to the Maignan and Mikol paper) that: (i) each such inhibitor is 'L'-shaped; (ii) the core has the two binding groups descending from it, one at each end of the L, and they are basically directed down into the S_1 and S_4 pockets.

(x) Maignan and Mikol – II

(Maignan, S. and V. Mikol, "The Use of 3D Structural Data in the Design of Specific Factor Xa Inhibitors" (2001) 1 *Current Topics in Medicinal Chemistry* 2003 161-174)

1054. Returning briefly to Maignan and Mikol, counsel for BMS elicited Dr Edwards's agreement to the following: (i) in the description of the S_4 pocket, just towards the end, they discuss the cation hole and that is the same cation hole that is talked about by Pauls and Ewing and (ii) when they discuss the S_4 pocket at p.170 (of the article) they point to a *"great diversity in the reported fXa inhibitors*...[being] *encountered in the P_4 group",* they are referring to the group that binds with the S_4 pocket.

(xi) Pauls and Ewing

(Pauls, Henry and William Ewing, "The Design of Competitive, Small-molecule Inhibitors of Coagulation Factor Xa" (2001) I *Current Topics in Medicinal Chemistry* 83-100)

1055. Counsel turned to the Pauls and Ewing article and brought Dr Edwards to various sections of it. Dr Edwards did not demur when counsel noted that within this article (at p.85) the learned authors (i) indicate that a variety of strategies can be deployed to optimise interaction with the S_4 pocket, and (ii) illustrate that fact with a series of modifications, one of which is compound 35, which was potent and selective.

1056. Counsel for BMS then suggested that from "*what we've just looked*" at (I believe that this was a reference to all the articles considered to this point, not just that of Pauls and Ewing) it was already becoming clear to workers in the field "*and they were realising and publishing*" that binding in the S_4 pocket could be achieved with different ways of interacting with the pocket, using a wide variety of different binding approaches. To this, Dr Edwards responded as follows:

> "*It certainly would be fair. I'm not sure* [about] *'wide variety of different binding approaches.' That suggests a very large number, whereas it presumably is limited to two or three different strategies, I would say. So, it certainly is more tolerant, that pocket.*"

1057. Dr Edwards agreed when it was put to him that it being a tolerant pocket "*was rapidly becoming well known*".

1058. Counsel for BMS next led Dr Edwards through the sections of the Pauls and Ewing paper where they (i) discuss a second structure-based approach that they took based on the established properties of the S_1 and S_4 pockets, and (ii) that this involved them engaging in structure activity relationships to design a molecule that they thought likely to bind, following the classic pattern of binding groups connected via scaffold. Responding to this, Dr Edwards indicated as follows:

> "*I wouldn't say they're contracting* [*sic* – constructing?] *structure activity relationships. Because they'd need the activity of the compounds a priori to feed into the design. I think what they're doing is adding in various groupings into whichever pocket, S_1 or S_4, and looking for potential interactions - are there any steric clashes, would it fit? It's not clear, all of their intentions in the design.... But they're looking for fragments which could be tolerated within the pocket....and [which], therefore, might be good suggestions. But in my experience, molecular modellers are not synthetic chemists and some of the time, or often, the suggestions are not worth pursuing. So, it would be natural [that] there would be a medicinal chemist available to help move through those list of compounds for really interesting ones. So, yes, it's a fairly standard approach to, I guess, design compounds that may bind and then, presumably, synthesise and test them and see if their hypothesis was clear.*"

1059. Proceeding through Pauls and Ewing, counsel for BMS elicited Dr Edwards's agreement to the following:

(i) they explain that certain aspects of the binding group were important, the methoxy group, whilst others, electron-withdrawing, such as the chloro, can be moved about;

(ii) their efforts led them to RPR120844, one of the products that Dr Edwards identified as significant;

(iii) the X-ray crystal structure of hydroxy-benzamidine trypsin was consistent with their hypothesis; they were doing other work in parallel to find alternative replacements of the naphthalene sulfonamides;

(iv) in totality, they adopted a systematic approach; synthesising molecules, testing them, using the structural and measured properties to drive the work forward to improve the behaviour of the molecules a process of design that is "*typically what you'd expect to see*";

(v) Pauls and Ewing found that "*the most efficacious intravenous pyrrolidinone inhibitors came from a combination of pyridylthiophene or thienopyridine P_4 group with an amino or hydroxybenzamidine P_1*";

(vi) they summarise the key inhibitors, one of which is 120844, and they then summarise, in the following terms, where they have got to:

> "*In the design of fXa inhibitors described above, several goals were achieved. An appropriate template, the pyrrolidinone scaffold, was found to yield potent and selective inhibitors of factor Xa. In addition, a collection of bicyclic and biaryl sulfonamides were identified which could be used to modify potency, physiochemical properties and in-vivo performance. Potency enhancements via substitution of the benzamidine or via heteroaromatic benzamidines were also achieved. Uniformly, however, inhibitors containing arylamidines resulted in low bioavailability when dosed orally in rats and dogs*";

(vii) they go on to explain their attempts to reduce the basicity of the molecule by replacing the amidine;

(viii) they achieved improvements with RPR208815, which had significantly increased oral bioavailability but a relatively short half life;

(ix) they decided to explore other azarenes as possible replacements for the benzamidines but this work did not lead to sufficient potency, although oral bioavailability was improved;

(x) in totality they could be seen to be "*working systematically through properties to improve the overall combination and reporting how far they've got*";

(xi) they moved to a further approach in which they used a different scaffold, ketopiperazine inhibitors, and they made a number of findings, one being that the molecule binds in the reverse mode when the scaffold is changed;

(xii) as the benzamidine was now binding to the S_4 pocket, they tried changing that;

(xiii) this led them to report RPR200443, compound 131, which had a K_i of 4 nanomolar, thousandfold selectivity against a panel of relevant serine proteases (which Dr Edwards agreed looked good under those parameters) and which was also coupled with good oral bioavailability and pharmacokinetics; and

(xiv) they describe that as a significant breakthrough in the search for oral factor Xa inhibitors, combining bioavailability and in vitro efficacy in one molecule and standing out as imparting favourable pharmacokinetic properties.

1060. Counsel noted that in his report Dr Edwards identifies RPR120844 rather than 200443, which, counsel suggested "*the authors themselves thought was the standout result of their work*", asking why Dr Edwards did not report 200433 also. The following exchange then ensued between Dr Edwards and counsel for BMS:

Dr Edwards:	*I thought that the previous compound was an interesting compound to exemplify the series and I didn't need to put all compounds, all possible compounds with any biological activity or ADME in vivo activity, oral bioavailability. So, it was simply to choose one analogue rather than another.*
Counsel:	*Can I suggest to you, Dr. Edwards, it's a little odd to review the report, the paper reporting this research, and pick from it not the molecule that the researchers themselves think is a significant breakthrough, but a different one because you think it's more interesting...?*
Dr Edwards:	....[I]*n looking at some of the data, it's encouraging. There's no further data to include how far it went into development. And if you look at the structure with the thiophene and the unhindered pyridine nitrogen and the pyrrole ring, it was obvious to me that this compound would suffer from metabolic instability and potential toxicity, idiosyncratic tox in the reactive metabolite formation. So, for those reasons, I looked at the structure and decided this wasn't something likely to succeed to market. And for those reasons, looking at the structure, it wasn't prioritised by me.*
Counsel:	*So, for all those reasons, which you didn't think to include in your report, you didn't include this one?*
Dr Edwards:	*And I've been given the opportunity to say that now.*

(xii) Zhu and Scarborough – II

(Zhu, B. and R. Scarborough, "Factor Xa Inhibitors: Recent Advances in Anticoagulant Agents" (2000) 35 *Annual Reports in Medicinal Chemistry* 83-102)

1061. Returning to Zhu and Scarborough, counsel for BMS noted that: (i) the learned authors discuss the DuPont work which preceded the 652 application; (ii) a series of structures described as highly potent mono-benzamidines with K_is in the low picomolar range "*provided lead structures for further development of nonbenzamidine factor Xa inhibitors*"; (iii) they pick up SN-429 (Compound 38) as an excellent illustration of that set of structures, which compound was a precursor to the widely discussed DPC423 molecule. The following exchange then ensued between counsel for BMS and Dr Edwards:

Counsel:	*DPC423 was a very well known molecule at the time, wasn't it?*
Dr Edwards:	*Yes.*
Counsel:	*You've established that from your research?*
Dr Edwards:	*Yes.*
Counsel:	*One of the ones that forms part of the agreed common general knowledge, it's listed in the agreed CGK document and Dr. Young says that it was widely noted at the time as a significant advance in the field. Would you agree with all that?*
Dr Edwards:	*Yes.*

(xiv) Quan and Wexler – I

(Quan, M. and R. Wexler, "The Design and Synthesis of Noncovalent Factor Xa Inhibitors" (2001) I *Current Topics in Medicinal Chemistry* 137-149)

1062. Turning to Quan and Wexler, counsel for BMS elicited Dr Edwards's agreement to the following: (i) that this was not early stage work; (ii) that their use of the rabbit arterio-venous thrombosis model to characterise the molecules that they were working on "*shows that they have evaluated and set up that model...*[and] *that they don't need to evaluate it further....*[and] [t]*hey don't need to validate it...by the time of 652, because it's already in use*". (Dr Edwards agreed in this last regard that the Quan and Wexler paper was published before 652 was applied for so it was clear that they were using this model and had validated it before 652 was filed); (iii) DPC423 has a phenyl group in the P_4 position; (iv) a medicinal chemist would see the lactam in P_4 as a plausible an isostere for the phenyl group; (v) one of the characteristics of DPC423 is that it has a relatively flexible core and one of the strategies that drug designers use to improve bindings (to give them greater rigidity) is to rigidify the core to increase the accuracy with which the binding groups are orientated towards their receptors, which sometimes works and sometimes does not; (vi) that rigidification is a well-known strategy, often employed by medicinal chemists, and it would not be surprising to find the team, in later work, using a more rigid central scaffold for their molecules; (vii) the 131 application (the prior art in this case) which is intervening work between 423 and 652, is characterised by the fact that what it describes is inhibitors with rigid bicyclic cores; and (viii) one can potentially see design and development history as a team works through different possibilities.

(xv) Zhu and Scarborough – III

1063. Counsel for BMS returned to Zhu and Scarborough, noting the DuPont work with the methoxyphenyl group in the S_1 pocket, the related observation that "*The para-methoxyphenyl group of 50a might insert into the small hydrophobic hole of factor Xa in the S1 site*", (p.92) and the modifications that lead to 50b, 50c and 51. Counsel for BMS put it to Dr Edwards that the para-methoxyphenyl binding in the S_1 pocket is the binding used by compound 18 of 652. To this Dr Edwards responded that "*In that S_1 pocket, potentially it may sit in a slightly different place. It may have a slightly different orientation which affects binding. But, yes, it appears to be in the same pocket, S_1.*" Counsel for BMS then noted that there are other reports of para-methoxyphenyl groups being used to bind in the S_1 pocket, several in the review literature and papers reporting particular lines of work, some of which Dr Edwards was taken through in his evidence-in-chief (considered above) and reported in his second report (appended hereto).

(xvi) Ries and Priepke

(Ries, U. and H. Priepke, "Factor Xa Inhibitors – a Review of the Recent Patent Literature" (2000) 3(12) *IDrugs* 1509-1524)

1064. Counsel for BMS turned next to the Ries and Priepke paper, with the following exchange then taking place between himself and Dr Edwards:

Counsel:	*If you* [look]*...under the heading 'Neutral factor Xa inhibitors' it's fair to say* [that] *this is an approach that was being...increasingly widely pursued in 2000 and 2001 to improve oral bioavailability?*
Dr Edwards:	...[I]*t was certainly being considered.*
Counsel:	*And we see the authors reporting the most prominent series of neutral inhibitors being the Eli Lilly series....We can start with molecule 54....That has methoxyphenyl binding at both ends?*
Dr Edwards:	*Yes.*
Counsel:	*So, one of those must be going in the S_1 pocket?*
Dr Edwards:	*Yes.*
Counsel:	*And...the Lilly binding model indicates that the right methoxyphenyl group occupies the S_1 pocket, while the left group*

binds to the S_4 pocket....[a]*nd...the upper section of the central phenyl is exposed to solvent. It doesn't have particularly effective binding, possibly because of the solvent exposure, is what they say.... If you read down...you see they made a change to give compound 55, and I think the change is made to the backbone....*[and the article says that this] *'gave greatly improved potency with a K_i of 12 nanomolar;....That indicates that changing the backbone to give surface interactions can improve potency?*

Dr Edwards: *Yes.*

Counsel: ...[T]*herefore, the overall binding of the molecule can be very substantially improved by selecting an appropriate backbone substituent?*

Dr Edwards: *It could be improved. The magnitude, I don't think you could say precisely and how you define 'substantial', but it can be altered....*

Counsel: *At 12 nanomolar, they've reached, not a bad result?*

Dr Edwards: *No....*

Counsel: *I'm just showing you examples to illustrate how the changes can work....*[t]*o...give the judge a better picture of how medicinal chemists designed....*[T]*his is the sort of thing you do....*[a]*nd can get very good results from?*

Dr Edwards: *Yes.*

Counsel: *A little further down...we see that the 4-methoxyphenyl group in the S_4 pocket can be substituted by a 3-amidinophenyl group with good binding results. Do you see that..?*

Dr Edwards: *Yes....*

Counsel: *We see a little further down that similar results have been reported by the DuPont Group with a slightly different structure?*

Dr Edwards: *Yes.*

Counsel: [Later] *we...see that a slightly different structure has been reported by Rôche with a 4-methoxyphenyl group....*

Dr Edwards: *Yes.*

Counsel *All these teams are trying to produce neutral factor Xa inhibitors to improve their oral bioavailability and pharmacokinetic properties while maintaining good binding, aren't they?*

Dr Edwards: *Yes*.

(xvii) Zhu and Scarborough – IV

1065. Returning to Zhu and Scarborough, counsel for BMS suggested to Dr Edwards that (i) the diversity of S_4 binding groups is highlighted by the variety of them which are reported, and (ii) compounds 32a to f show the diversity of binding groups which can be used in this pocket, giving similar potencies with one exception? To this, Dr Edwards responded that there was certainly a change in structure but that he would not say that it was "*a large diverse set, looking at the basic groups and the cyclic rings*". Counsel for BMS also noted that the article identifies a further set of different S_4 binding groups which enjoyed high potency (nos. 79-82). The following exchange occurred concerning the S_4 pocket, the P_4 elements, development issues, and the balance that needs to be struck between potency and physiochemical properties:

Counsel: [T]*hey point out that the S_4 pocket is much more tolerant of structural variations?*

Dr Edwards: *Yes.*

Counsel: *And that the diverse P_4 elements, further down, provide opportunities to modulate the physiochemical properties, which are the ones which deliver the desired in vivo antithrombotic efficacy in pharmacokinetic profiles?*

Dr Edwards: ...[I]*f the compound is metabolically unstable it won't be able to be efficacious. So, it's listing some properties but not all.*

Counsel: *The teaching, the learning is very clear that you can use changes in the S_4 pocket to improve your bioavailability and pharmacokinetic profiles while retaining binding, because the S_4 pocket is relatively tolerant or liberal in what it will accept?*

Dr Edwards: *Yes....*

Counsel: [They also sum up] *the balance that has to be struck between potency and biological characteristics. You need to balance them in order to get an effective oral therapy?*

Dr Edwards: *Yes.*

Counsel: *The balance is what the researchers a* [sic- are?] *looking to achieve, it is a trade-off between potency and balance physiochemical properties. Potency is merely one factor. It is essential but is not one from which alone success can be predicted.*

Dr Edwards: *Yes.*

(xviii) Maignan and Mikol – III

1066. Returning to the Maignan and Mikol article, counsel for BMS elicited Dr Edwards's agreement to the following:

(i) this is a review article that Dr Edwards considered to be a seminal paper in the field at the priority date;

(ii) it is fair to describe the paper as containing a clear and comprehensive exposition of the knowledge which can be gained from 3-D structural data in designing an effective and specific factor Xa inhibitor;

(iii) it likely would have been required reading for a medicinal chemist entering the field at the time;

(iv) though it would not be the only thing of importance, it would teach the medicinal chemist a great deal of what they needed to know in order to design a research programme, with the learning coming from both the information in the paper and the material to which it refers the reader; and

[Selectivity]

(v) Dr Edwards recognises the importance of the paper – so much so that counsel for BMS put it to Dr Edwards, and demonstrated, that elements of Dr Edwards's report repeated elements of Maignan and Mikol, albeit that Dr Edwards's ultimately disagreed with what those learned authors had to say about selectivity (they indicated that while selectivity was initially thought to be a challenge it had been resolved in most cases). At this juncture, the following exchange occurred between counsel for BMS and Dr Edwards:

Counsel: *I don't mean to be critical, but without any indication or acknowledgement, you have quoted from this paper, you have then made a statement which is, by and large, contrary to what the authors of the paper are suggesting about selectivity. And you have not acknowledged that in that respect you are contradicting what the authors teach. Could you possibly*

	explain why you thought it appropriate to do that?
Dr Edwards:	*I don't believe I am contradicting. It has been resolved in most cases, not all cases. And that's what I'm saying, if you're running a programme with new compounds being made, you can't guarantee that in all cases it is selective. So, I believe my statement is consistent with what is written in the paper.*
Counsel:	*Don't you think it might have been a little more frank to have acknowledged that that challenge had been largely resolved?*
Dr Edwards:	*Not necessarily. I think it's important to point out that it is an issue for any project to consider.*
Counsel:	*...I'll give you one more opportunity because I'm going to submit to the Judge that the way you have formulated this in your report is slanted to paint a picture which is actually rather different from the picture that the paper, read fairly, paints, and if you'd acknowledged that you were moving away from what the paper says, it would have been of assistance to the Court....*
Dr Edwards:	[A]*s a medicinal chemist*[ry] *principle, if something is similar there's a chance that selectivity may be difficult to achieve....I was making a general point....*
Counsel	[Y]*ou are giving a rather different impression from the impression given by this seminal paper about the extent of the issue of selectivity and that you don't acknowledge that fact.*

1067. Counsel for BMS also noted that Dr Edwards's report repeated elements of Maignan and Mikol when it came to diversity in the reported factor Xa inhibitors.

1068. Counsel noted the observation in Maignan and Mikol that "*very importantly the fXa/inhibitor models are usually in good agreement with the experimentally determined structures*", (correctly) rephrasing this in his own words as meaning that modelling usually has predictive powers, something noted by Dr Edwards in his report. At this juncture the following exchange occurred between Dr Edwards and counsel for BMS:

Dr Edwards:	*I don't dispute that it can work but sometimes it doesn't...*
Counsel:	*Most of the time it works?*
Dr Edwards:	*Most of the time....*
Counsel:	*Modelling is a good place to start, isn't it?*
Dr Edwards:	*It can be....*
Counsel:	*And it usually works, that's what they* [Maignan and Mikol] *say*?

Dr Edwards: *It usually works...but it's not a guarantee....*
Counsel: *We're not talking about guarantees...we're talking about reasonable predictions.*

1069. Counsel noted that Maignan and Mikol suggests that there is a wide variety of groups that bind in the S_1 pockets, binding P_1 groups, the central scaffolds and the S_4 pocket binding P_4 groups. And he noted that they point out that one starts highly basic, and then goes on to the moderately basic P_1 groups and then the neutral P_1 groups. Counsel for BMS suggested that what Maignan and Mikol were doing in this regard was showing the development as the researchers try to balance binding properties with biological properties. Dr Edwards indicated in reply that he did not know the chronology but accepted that that "*looks like the chronology*".

1070. Counsel noted that that the S_4 pocket has a size and shape which makes it suitable to accept large binding groups such as a ring structure. Dr Edwards accepted that the S_4 pocket is more tolerant. Counsel then put it to Dr Edwards that there is a significant number of possible binding interactions which could be tried within the S_4 pocket. To this, Dr Edwards responded that "*there are a limited number of different types of interactions, the anionic hole, the amino acid backbone. We've talked a little bit about some of the groups. There is a limit to this. I wouldn't say it's significant, but there are different strategies that can be tried.*"

(xix) Patent Application 652.

1071. Counsel for BMS observed that that the application discloses a very large number of molecular structures, though suggesting that "*They do all have some things in common: They all have in common that the structure, which has been widely researched and described, P_1-core-P_4, is present in all the embodiments, isn't it?*" Dr Edwards confirmed that this was correct "[a]*s far as I can tell*".

1072. Counsel for BMS then turned to the embodiments in the patent application and what might be styled his 'narrowing down' point, *i.e.* (as he put it himself):

> "*What we're going to see, as we go through the embodiments, is that they become more and more focused until you get down a relatively limited range of molecules, where you can see that a particular structure is defined and the substituents are rather fewer in number and the take-home message is: This is our target and it has certain properties.*"

1073. I do not see that there is the successive narrowing to which counsel for BMS refers. This point was expressly confirmed by Dr Young when he was under cross-examination:

Counsel: ...[T]*here's a specific point I wanted to put to you, which was that it had been suggested that there was a progressive narrowing in the patent application. That's not strictly correct, is it?*
Dr Young: *Well, there are 74 compounds in Embodiment 8 and, you know, as many as you like almost still in Embodiment 7. So, we are narrowing in the total scope. But we have six compounds in Embodiment 8 that are not in Embodiment 7*".)

1074. In any event the following exchange occurred between counsel and Dr Edwards at this juncture:

Counsel: [Dr Young in his report] *starts to describe the embodiments using the notation in the specification and what we see is the P_4 and M_4 binding groups with the scaffold or core in the middle, P, M, yes? ...If you open the application you'll find Embodiment 1?*

...Embodiment 1 has an M_4 group described by the Formula Z-A-B....[a]*nd B is defined at page 10, with a ring structure....And as Dr. Young says in...his report....*[t]*his is a lactam which may be substituted with sulfur as well and I understand those are called sultams? ...As Dr. Young says...the focus of the application, therefore, is a lactam in the S_4 binding position, P_4 of the molecule?*

Dr Edwards: *....The lactam is certainly noted in the patent.*

Counsel: *So, if we move on to Embodiment 2....we are immediately down to a bicyclic core, aren't we, two rings fused together?*

Dr Edwards: *Yes.*

Counsel: *Otherwise it's the same as Embodiment 1?*

Dr Edwards: *It's certainly bicyclic. It would appear to be similar in other respects.*

Counsel: *Embodiment 3....narrows down the rings in the core to the illustrated examples?*

Dr Edwards: ...[A]*t least one side of them, there appears to be broken bonds to the left of the structures.*

Counsel: *The ring M is shown and then on the following pages the ring P, starting at 34....*[s]*o, both rings are reduced to a number of examples, and you can count them or take it from me that there are now 85 rings for M and 44 for P, the two being fused together?*

Dr Edwards: ...[Y]*eah.*

Counsel: *The binding group G in the original Embodiment 1 is narrowed down to the example starting on page 36....*[t]*he first of which is the para-methoxyphenyl, isn't it? ...*

Dr Edwards: *Yes, that list then proceeds for –*

Counsel: *There's 160 of them....*[With] *Embodiment 4....*[w]*e now find that the core rings have been narrowed down again, there are now 65 M rings, fused to 26 P rings?*

Dr Edwards: *Yes.*

Counsel: *The number of G substituents, which we pick up at page 49, has gone down to 81. B is defined substantially as before. Embodiment 5 starts on page 54....*[a]*nd by this stage there are now even fewer possibility for M and P, there are 55 Ms and 15 Ps. G_1 in the G_1G group has gone and G is reduced to 58 examples, which are shown starting at page 57.*

Dr Edwards: *Yes.*

Counsel: *And at the other ends, Z-A-B and Z has gone; A is selected from the 11 options at the foot of page 58; B, over the page, is a range of six and seven-membered ring lactams totalling, I think I'm right in saying, 56, if you allow for R^{4a} substituents and R^{4c} listed as being placeable if the rings. R^{4a} and R^{4c} are, I think, defined in Embodiment 5. Back at page 53 and 54. So, we're going down steadily. Embodiment 6 at page 63, narrows the options still further.*

Dr Edwards: *Yes.*

Counsel *....So, the core has now narrowed right down, hasn't it?*

Dr Edwards: *Yes.*

Counsel: *The P_4 and M_4 designations are retained. On page 65, P_4 is G and M_4 is A-B....G is selected from that rather smaller number of substituents on page 66, 27 possibility* [sic?]. *And A-B is selected from the lactams on page 66 and 67, the last two rows of which are sultams?*

Dr Edwards: *Yes.*

Counsel: *Embodiment 7 starts on page 67 we now have a specific two-ring*

fused ring structure. So, we've defined the core, haven't we?

Dr Edwards: *Yes.*

Counsel: *And the substituents, P_4 is G for Embodiment 6, which is one of the 27 possibilities, and M is A-B, selected from the two options on page 68....*[t]*he left one being the one found in Example 18?*

Dr Edwards: *Yes.*

Counsel: *Embodiment 8 is a list of 74 specific compounds. They run from page 68 to 76, there are 74 of them. And you were taken this morning to the one at the foot of page 69, which is Example 18, or apixaban?*

Dr Edwards: *Yes....*

Counsel: *Embodiment 9 starts a new group of compounds at the foot of page 76. The key change of the group of Embodiments 1 to 8 is that these have a single ring core structure rather than the two rings, do you see that, ring M?*

Dr Edwards: *Yes.*

Counsel: *Those embodiments run from 9 to 15. I'm not going to go through them in detail. With a change from the fused bicyclic ring core to a single ring core they essentially mirror the first group, with increasingly narrower options for the core ring and appended binding groups. Finally, at page 129, there's a list of alternative substituents which gives some more possibilities in particular circumstances.*

Dr Edwards: *Yes.*

Counsel: *Now, that's the disclosure of the embodiments in the application and I now need to take you to the detailed discussion of those embodiments and what we say a medicinal chemist gets out of it.*

(xx) Synthesis

1075. Counsel turned next to the synthesis section and suggested to Dr Edwards that what is made clear is that the authors recognised that potent binding with factor Xa was what was being looked for, "[b]*ecause it says compounds of the invention have K_is of less than 10 micromolar, preferred are less than 1, more preferred are less than 0.1, even more preferred are 0.01, and still more preferred compounds have K_is of 0.001. And that's the sort of target that...one is actually looking for..?*" Dr Edwards agreed that this was so.

1076. Over the course of a series of questions, counsel for BMS elicited Dr Edwards's agreement to the following: (i) while the specification states that initial screens show compounds having K_is below 10 micromolar, 10 micromolar is simply a starting point that enables one to remove anything that it is known will not be useful; (ii) the difference between 0.001 micromolar and 10 micromolar is four orders of magnitude, and if one had that level of difference between binding to factor Xa and binding to thrombin, one would have ample selectivity to make the molecule attractive; (iii) turning to p.188 and looking through the examples and syntheses it would be fair to state (Dr Edwards responded "[g]*enerally*") that those examples and syntheses were set out in a way which would enable the reader to review and repeat them with reasonable facility, if desired; and (iv) that with the exception of Example 18, all of them had been made in quantities of less than a gram. When it came to point (iv), Dr Edwards did not, however, agree that it would be fair to say that if one goes through the worked examples, Example 18 stands out as having been made in substantially larger quantity than any other. When this was put to him he responded "*No, not substantially. It's been made in a greater quantity, but it's a low, it's still a low quantity overall, a couple of grams. To me as a medicinal chemist, that isn't a great difference.*" He did accept, however, that it was about five or six times as much as any other example. Moving on in a similar vein, the following exchange occurred between counsel for BMS and Dr Edwards:

Counsel: [Example 18 is] *a very low yielding synthesis overall, isn't it?*

Dr Edwards: *It is. But that's perfectly common. As I think I mentioned, the idea for medicinal chemistry, to generate a compound, is to get to it and test it, get to it quickly so that it's not lost in the SAR data that other compounds and other sub-series are generating and so it still remains relevant. It's certainly, in my experience, not ever the case that a medicinal chemist, at this stage, would try to optimise a reaction from yield. To a degree, they do that because you need some material and if you could do something very simple to increase the yield, you would do that. But it's not a sustained effort. So, the fact that it's 1.3% overall is not unusual.*

Counsel: *I understand that. But if you're making 3g in a yield of 1.3%, you have quite a lot of starting material and it takes quite a lot of work?*

Dr Edwards: *It does. But they could've been making that for use for some of the intermediates, in library chemistry, for example, so...*

Counsel: ...[I]*f they were going to use it as a sort of stock product, you might expect them to think about optimising the synthesis so as to get a better yield?*

Dr Edwards: *Not necessarily. The idea is to exemplify. So, I could give you an example, part D product...*[I]*t was perfectly common at that time, and still is, to outsource the root to a contract research organisation whose job is to scale up and provide greater amounts of template. That resynthesis and scaling up is not a medicinal chemist's job, that's designing compounds. So, it's perfectly possible they have a functioning research route that they could develop to get to part D, which is then outsourced to a CRO, a contract research organisation, to scale up and provide the material....*

Counsel: *It still takes a lot of work, doesn't it, Dr. Edwards? And particularly the step combining part B and part C to get part D is carried out on quite a small scale and has to be repeated numerous times to get the quantity at the end, because it's low yield and small scale?*

Dr Edwards: *Yes. But I don't know how many times this reaction was repeated, I don't know if this was the largest scale that was used.*

Counsel: ...[Y]*ou'd think if they had done it on a larger scale, it would appear in the example, wouldn't it?*

Dr Edwards: *...I would've thought if they were characterising the compound properly, because this is an important compound for them, they would've put the purity data, they would've put a high res mass spec or a CHN analysis, more data than they have. So, I don't think it's possible to assume that that is the case.*

Counsel: *So, you think that, even that that is the synthesis as they describe it, that isn't what they did; is that what you're saying?*

Dr Edwards: *I don't know. I can only say that it's possible....*

Counsel: *If they did that, they had to repeat that step, combining part B and part C, over 100 times to get 3g at the end, didn't they?*

Dr Edwards: *Theoretically. But I think it's highly unlikely they would've run a reaction 100 times. Because if it takes, say, 24 hours - and I don't know how long the reaction takes without looking - let's say a day, that's 100 days. That's a long time for any work to stand still to generate a final compound, where, as I say, all of the other SAR is more moving along. I've never heard of that. It could be they generated, you know...0.7g or 0.17g and outsourced this to a CRO for them to scale up and they –*

Counsel:	*It could be that they did it in parallel repeated times?*
Dr Edwards:	*It could be. It's possible. It's highly unusual to do 100 reactions like that in parallel, but it is possible.*
Counsel:	*And if they did, it was a great deal of work..?*
Dr Edwards:	...[I]*t would be an effort. But I think if you look at every compound as a final compound in a patent, it's also a great deal of effort.*

1077. Counsel for BMS turned next to where Dr Young in his evidence discusses Embodiment 8, explaining that it contains a list of 74 preferred compounds, and sets out a diagrammatic representation of the 74 compounds and how they relate to each other. The following exchange then ensued between Dr Edwards and counsel for BMS:

Dr Edwards:	[T]*he diagram is potentially missing important information, which doesn't allow me to make an informed opinion. For example, the R_3 group, we have 33 examples out of 74. It's not clear to me if the remaining 41, if that is correct, examples are 41 different substituents or one 41 with a frequency count of 41 one substituent, which might make it important. So, if you were doing this analysis for real, you would have that count. So, I feel that this is a partial explanation of the activity that might be undertaken, it doesn't give me full information, so I can't make an informed choice.*
Counsel:	*The evidence makes clear that he has put the two most common R_3s in the diagram, so that all the other R_3s are in smaller numbers....*
Dr Edwards:	[T]*o me...*[his text] *could also read he's focusing on two groups from the R_3 set, not the R_3 set is predominantly encountered....*
Counsel:	[W]*hat we see is a picture that shows 66 of the 74 structures are within Embodiment 7....You wouldn't disagree with that, would you?*
Dr Edwards:	*No.*
Counsel:	*What I understand your evidence to be is you disagree with Dr Young's use of the words the skilled medicinal chemist would quickly recognise what he says?*
Dr Edwards:	*...I believe they come from names. So, it would be an effort to convert the names to structures to then do this activity, which itself is time-consuming and difficult and mistakes can be made, with the best of intentions....*[I]*t's not a trivial exercise....*
Counsel:	[Y]*our disagreement with Dr Young is not that the skilled medicinal chemist would recognise this pattern, but with the amount of effort required to do so?*
Dr Edwards:	*Yes.*

1078. Over the course of a series of questions, counsel for BMS elicited Dr Edwards's agreement to the following: (i) all 74 of the compounds have the common core (core 74), that being the core of Embodiment 7; (ii) 73 had the P_4 proximal PR ring; (iii) 66 have the $P_4$4 lactam, being one of the two forms of AB shown on page 68 of the application; (iv) of those, 43 are the saturated ring and 23 are the unsaturated ring; (v) with regard to the P_1 substituent (which binds with the S_1 pocket) 44 of the 74 have the para-methoxyphenyl group; (vi) as regards the group labelled R_3 that corresponds to the group R_1a in the embodiments of the specification, with Dr Young using the standard IUPAC nomenclature; (vii) the two most common are carboxymethyl and trifluoromethane (the latter of which is the substituent used in DPC 43); (viii) the bigger changes are being made on the R_3 group, with the P_1 group also being looked at.

1079. Counsel for BMS subsequently brought Dr Edwards to Dr Young's observation that "*A skilled medicinal chemist would recognise...preferred substituents and where changes were focussed to secure potency and/or optimal pharmacological and physicochemical properties*". This

led on to something of a consideration of frequency analysis and (from an Irish patent law perspective, irrelevant) the proposition that the fact that it was a BMS team would play into a medicinal chemist's assessment of their labours. It is useful to quote elements of the exchange between counsel for BMS and Dr Edwards that arose at this juncture:

Counsel:	*You say that one* [of] *the most frequent substituents is carboximide, which is a polar substituent..?*
Dr Edwards:	*It is.*
Counsel:	...[I]*t has the potential for h-bonds with the target enzyme?*
Dr Edwards:	*Yes....*
Counsel:	*Just for your reference, Dr Yudkins, who gave evidence for Teva in Sweden...agrees with that....You will recall reading that he agrees with that..?*
Dr Edwards:	*Yes.*
Counsel:	*So...as a skilled medicinal chemist looking at this, you would see a relatively frequent use of a substituent...capable of hydrogen bonding to the surface of factor Xa..?*
Dr Edwards:	...[T]*here's two points to make here. One, the CF_3 group is a very desirable group in drug discovery....$CF_3$3 groups are something medicinal chemists search for and would want to include in their compounds to see what happens....The primary carboxamide can, in principle, make those interactions we've just discussed....But I think we shouldn't forget that the purpose of...frequency analysis, in the absence of any real data, is to identify the most likely compound or compounds of interest, and that would be the CF_3....*
Counsel:	*I think you're approaching this as if only one molecule could...be derived from this analysis...*[C]*an I suggest to you that a fair-minded reader...would think that both carboxamide and...CF_3, are interesting substituents of the R_3/R_1a position?*
Dr Edwards:	*They would be interesting substituents, yes.*
Counsel:	*And the manipulation of that substituent indicates that the workers are aiming to fine-tune the physiochemical properties of the molecule?*
Dr Edwards:	...[P]*otentially, yes.*
Counsel:	*This is the sort of compromise stage where you adjust substituents on the molecule to see what effect it has? You've just described the attractiveness of the CF_3 group. What we see here, I suggest...is a pattern of work which indicates that the team are trying various substituents to see how they perform in order to identify which particular set of compromises gives...the best overall result.*
Dr Edwards:	...[P]*otentially but...it's still guesswork, because there's no discernible SAR in the patent....*[T]*his is a surrogate approach to try and find some useful information....*
Counsel:	...[T]*hey would not be doing this work in this way if they didn't have a good reason...would they?*
Dr Edwards:	*I suppose they have reasons to do it. I couldn't speculate....I don't know the issues and the SAR they had and why they were designing particular compounds....*
Counsel:	*...You know this team are working to produce an effective factor Xa inhibitor – the title of the document tells you that. They're a team who are well known in the field, they have done a lot of work and they have done it very successfully....And when one sees them doing work of this pattern, the conclusion of...an open-minded medicinal chemist would be it is likely that they have found something they consider to be of value in their search?*

Dr Edwards: *That's certainly something they may think....*

Counsel (Teva): Judge...the identity of the patentees is, as a matter of Irish law, not relevant. [This, I respectfully note, is correct].

Counsel (BMS): *If they hadn't found something of value in their search for a potent and selective factor Xa inhibitor, the work that is apparent from Embodiment 8 would be a waste of time and effort, wouldn't it?*

Dr Edwards: *Well, they publish a patent which claims certain chemical space, which presumably would represent prior art and stops another company getting into that area. So, it's sometimes used, in my experience, that you publish just to stop someone else getting into your area....*

Counsel (BMS): *Well, the specification does say they have done some testing work...so, you can't say that they have done no testing....*[T]*hey just don't put the results in.*

Dr Edwards: *...*[I]*f the specification indicates they've done testing...I would have to assume that they have. But from the level of potency described, perhaps I would infer that they're not efficacious factor Xa inhibitors.*

1080. Counsel for BMS then brought Dr Edwards through Dr Young's analysis of Figure 18, basically putting the same propositions that he had put in relation to Figure 17 and receiving substantially the same answers.

1081. Next, counsel for BMS looked at the comparison with 131 (in the corrected version of Figure 19 in Dr Young's statement). Over the course of several questions he elicited the agreement of Dr Edwards to (i) there being (a) considerable variety in the P_4 position and (b) no lactams (as regards (b) it was more a case that Dr Edwards accepted the word of counsel for BMS that this was so), (ii) there being no example which is less than two changes away from any of the worked examples in 652 (as regards (ii) it was again more a case that Dr Edwards accepted the word of counsel for BMS that this was so), and (iii) the lactam in 131 being found only in the Markush formula. As to counsel's related proposition that there was nothing in 131 which points the reader to Example 18 of the 652 application, Dr Edwards responded that that was something of which it was "*difficult...to be absolutely certain. There's nothing that points to it. It doesn't encourage a route to a lactam substituent, if can I put it that way.*"

1082. Counsel for BMS then turned to a consideration of Dr Young's summary of his reasons for concluding that Example 18 is rendered plausible by the contents of the specification (which Dr Edwards had been taken through during his evidence in chief). When it was put to Dr Edwards that the reasons were cumulative, with none of them individually giving the answer, but which (viewed cumulatively) led Dr Young to the view that it can be seen that Example 18 could reasonably be thought to be likely to work, Dr Edwards responded that "[T]*hat assumes that each of the preceding points are correct. And I would argue it's speculation at each point. So, I'm not sure I would draw the conclusion that it's likely or reasonable. I think it's speculation.*" This led to the following exchange between counsel for BMS and Dr Edwards:

Counsel: *Let me put it to you like this....What Dr Young is saying is, when you take all these indicators together, a skilled medicinal chemist approaching this document with an open mind would reach the conclusion that these workers had done some work which gave one a reasonable basis for thinking that it was likely that Example 18 might be worthwhile.*

Dr Edwards: *If I make the assumption that it is an uninventive person that has knowledge of the area that this is addressed to, I find the five...or six...steps that are combined to be outside of the remit of someone who is...uninventive....*

Counsel:	...[W]*hy would you say you need to be inventive to...?*
Dr Edwards:	*Because these are very difficult assumptions to draw and build upon in a sequence of six things that you need to put together to come to an answer. So, I feel that isn't something that someone who is uninventive would be able to do.*
Counsel:	*What do you mean by 'uninventive'? It's not creative, it's analytic, isn't it?*
Dr Edwards:	*Yes, but someone who is an uninventive scientist in the area I'm not sure would be able to come to the conclusion that each of these points is guesswork and that you combine them to come through. So, theoretically, if you were to believe each of the points and build one from the other, theoretically it's possible. But lots of things, in theory, are possible but in reality may not be the case.*
Counsel:	*In theory it's possible?*
Dr Edwards:	*In theory.*

D. Re-Examination

1. Literature Reviewed

1083. Asked by counsel for Teva (i) to confirm that he had received all of the literature that was exhibited to the witness statements of Dr Young, Dr Edwards confirmed that this was so, (ii) whether there was anything in that literature that would have caused him to alter in any way the content of his witness statements, Dr Edwards confirmed that there was not.

2. Structural Recognition Skills

1084. Following on a consideration of the topic of structural recognition skills, Dr Edwards was brought to §118 of the agreed CGK document, where it is stated that "*Often relatively small modifications can result in significant changes in activity against the target enzyme or against other enzymes.*" Asked by counsel for Teva to explain this sentence and whether it agreed with his own evidence, Dr Edwards responded as follows:

> "*I believe it agrees with my own evidence. And I accept the agreed CGK document. So, I think I provided, in my witness statement, several types of very small changes that a compound could have. And I think that was further noted in Appendix 1, that I went through a couple of compounds where you can make a single small change to the compound and change the activity against the primary target, in this case factor Xa, and potentially against related enzymes. And I further gave the example of Merck's Januvia, where they changed the CH_3 for a CF_3 and dramatically altered the properties, the biological properties of the compound.*"

1085. Counsel for Teva noted that Dr Young, in his expert report, agrees that even small chemical changes can have material effects, then moved on to the topic of 'modelling', asking Dr Edwards what is meant by this term. To this, Dr Edwards responded as follows:

> "*Molecular modelling...is a computer-based technique to try and capture the structure of an enzyme, a protein, binding pockets and ideally recapitulate what you would see if you had an X-ray structure, which is more of the gold standard.... We know at this time, although I think they potentially existed, getting routine X-ray structures of compounds bound to factor Xa was difficult or impossible. I believe that came later. So, you might use something called a homology model; you might take a related serine protease, like trypsin, for example, for which you do have an X-ray and you would chain the relevant amino acids in the protein chain and model that to a lower energy confirmation and it would twist the protein, and then you would get a slightly different*

shape in binding pockets, potentially. And that is what you would use to dock compounds in. So, you take your inhibitor, get a lowest energy confirmation, or a low energy confirming and, using a computer, add that compound into the binding pockets. It can work, but it's difficult sometimes, because it's guesswork, using homology modelling, that you are really replicating the architecture of the pocket. And we know that if we're off by even a small number of angstroms or fractions, you can affect the strength of interactions like vent valves and hydrogen binding. So, potentially even small unintended errors in the structure could lead to poor design because you're not docking correctly."

3. Identification of Compounds of Interest

1086. Asked by counsel for Teva to explain how certain compounds in his first witness statement at §6.46.2 were identified by Dr Edwards from the papers as being of particular interest, Dr Edwards responded as follows:

"*I used my assessment of which compounds were showing properties that may set them aside from the common stock...I took the view that I didn't want to spend days and days and weeks doing this and delving down into other papers, because in the project team that may exist, you wouldn't work in isolation. You would certainly have a lot* [of] *literature yourself as the medicinal chemist, but very soon you would be talking to other team members and taking their information, knowledge, they would be sharing papers. So, I think it's a more reasonable approximation to the real world by looking at a literature search, the primary hits returned from that and not necessarily trying to obtain every single reference relating to factor Xa.*"

4. Zhu and Scarborough

1087. Asked by counsel for Teva to confirm that compound RPR-120844 as referred to by Zhu and Scarborough is the compound referred to by Dr Edwards in his witness statement, Dr Edwards indicated that this was so. Asked to confirm that RPR-200443 (as identified by Dr Young) is a different compound, Dr Edwards confirmed that this was so.

1088. Dr Edwards was asked by counsel for Teva to read the below-quoted paragraph from the Zhu and Scarborough article and asked if he agreed with it (Dr Edwards indicated that "*I think I agree with it*"):

"*However, due to the symmetric nature of the S1 and S4 pockets (both S1 and S4 pockets can bind to hydrophobic or positively charged motifs), it is sometimes not obvious how to predict the binding modes...of specific inhibitors with factor Xa. Additionally, a subtle structure change of a lead structure can reverse the binding orientation. It might also be possible for an inhibitor to have dual binding modes. Thus, within a series it may be difficult to carry out systematic structure-activity relationships if the binding orientation changes due to very subtle structural modifications or an incorrect binding mode is presumed.*"

5. Writing Out Compounds

1089. Turning to the issue of "*writing out compounds*", counsel for Teva asked Dr Edwards to discuss how a medicinal chemist would usually expect to see compounds represented and why. To this, Dr Edwards responded that "*We're* [*i.e.* medicinal chemists are] *very much structure-based. So, diagrams/pictures. I would expect, more often than not, to see structures written out. Names can be tricky things to reduce to a structure, particularly if it's complicated.*"

6. The Patent Application

1090. Turning to the substance of the patent application, counsel for Teva asked Dr Edwards to give an overview of what is claimed by that claim 1 of the patent application. Dr Edwards responded as follows:

> "*So, P_4-P-M-M_4....*[I]*t's a very broad structure. There's no focus on a lactam in that structure. I might, as I think I said yesterday, if...*[there] *was really an intent to focus on lactams, I might expect to see the ring system within one of those P_4 or M_4s, for example. But it's just a very broad Markush structure.*"

1091. Asked by counsel for Teva to go back to Embodiment 1 in the application and to identify any overlap/relationship between claim 1 and Embodiment 1, Dr Edwards indicated that "[I]*t looks like Embodiment 1 has the same Markush structure as claim 1*".

D. Further Cross-Examination

1092. Though matters ought to have ended with the re-examination, counsel for BMS suggested that there was one issue which had arisen in the re-examination (re. modelling) that did not arise from the cross-examination and was not in the evidence-in-chief (though this was disputed by counsel for Teva). I allowed counsel for BMS to ask a couple of brief questions concerning the Maignan and Mikol paper, which Dr Edwards agreed, initially from memory and then from a brief examination of same, is a paper based on experimentally-derived structures and modelling.

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The Evidence of Dr Young

A. Introduction

1093. Dr Young is a distinguished medicinal chemist with over 30 years' experience in drug discovery. In his first witness statement, Dr Young states (at §8):

> "*I was asked by McCann FitzGerald LLP, on behalf of BMS, to provide my opinion on the following: A. the person or persons to whom the Patent is directed (the 'skilled person'); B. the common general knowledge of the skilled person at 21 September 2001 (the 'Priority Date'); C. what would have been plausible to the skilled person concerning apixaban on the Priority Date based on the Application and the skilled person's common general knowledge; and D. if apixaban would have been obvious to the skilled person on the Priority Date starting from WO 131.*"

1094. Subject to para.4 of this judgment an abridged version of Dr Young's written evidence is set out at Appendix 16. I respectfully invite readers of this judgment to read that appendix and then resume reading here. An account of the evidence that Dr Young gave when examined, cross-examined, and re-examined follows hereafter.

B. Examination

1. Some Minor Corrections/Embellishments

1095. Counsel for BMS brought Dr Young to his witness statements, got him to confirm that they were his, *etc*. Then Dr Young brought the court to a small number of minor corrections.

1096. At para. 48 the following correction, as described by Dr Young, required to be changed as regards his consideration of compound 4, a correction which also led on to the following exchange between counsel for BMS and Dr Young:

Dr Young:	[A]*s was pointed out to me under cross-examination in Oslo, I'd inadvertently...put the wrong number in in terms of the activity of the compound....*
Counsel:	...[C]*an you...tell us why you chose that particular molecule, compound 4?*
Dr Young:	*Because it was one of a...series of molecules that a lot of people looked at and...it shows how quickly you could combine different parts of material in this combinatorial fashion that is spoken about in the reviews and in my report and...how quickly you can make some of these compounds and how efficiently you could study your SAR, and other things.*
Counsel:	...[C]*an you tell us what the binding groups are?*
Dr Young:	...[I]*f we look at 357...if you look at the black figure with a little bit of colour in there, the green lines in this are the molecule. That is compound 4. All of the white things around it are the amino acid residues in the protein, in factor Xa. And what we see here is a proposed binding mode of how the pyridine part of the molecule, which is the bottom most bit, as you look at it is – I'll use a Welsh term here - it cwtches nicely* [cwtches: pronounced 'cutches', *i.e.* to cuddle (used here to suggest 'fits in' nicely)]....*You have this box*

that you fit into nicely....So, that's how we can see that part of it, the proposed binding mode. And then the theory would be that the other part of the molecule would go into the S_1 pocket....

Counsel: ...[W]*hat's the binding group in the S_1 pocket in that molecule?*

Dr Young: *It's the para-methoxyphenyl. It may be called benzole here because of the connectivity....*

Counsel: *Now, later on in your statement you produce – you've put three figures on page 28, which is page 166 of the book, it's Figure 17, then on page 30 there's Figure 18, and slightly further on on page 35 there is Figure 19. And if you take the bundle of cross-examination materials for Dr Edwards at tab 4, there are some further representations of those figures. And can you just explain what's happened here?*

Dr Young: *Yes, so two things happen. Ahead of my examinations in Sweden, I went through and I recounted the frequency of some of the groups that were there. I basically had an Excel file with how I recorded the data. And I just realised that I'd miscounted them on a couple of them. It doesn't have any effect on the material output of this. You know, we're looking at 42 and 43 and then 22 and 23, rather than a big difference. It doesn't impact the overall sentiment of what I found in the analysis. But I was just trying to be correct with the numbers.*

1097. Dr Young also had some further minor corrections and added a brief word on his professional experience.

2. Preparation of Evidence

1098. Counsel for BMS brought Dr Young next to how Dr Young prepared his evidence in this case. This led to the following suite of exchanges between counsel and Dr Young:

[a. Initial Work]

Counsel: *Can you just run us through the sequence of events that occurred when you were first contacted and asked to give evidence?*

Dr Young: *....So, the first contact was an e-mail from Matthew Shade of WilmerHale asking to speak to me, saying that I had been recommended by a good friend of mine, Paul Leeson....[W]e had a first interview, I spoke to Matthew, he asked me some questions. He wanted to read through some of my own work and my own publications on factor Xa, he had a few things he wanted to clarify. And I basically got cross-examined for the first time, I think it's fair to say. And after this he said... 'thank you, I think you can help us here.' ....The first thing I did was I prepared a report about the state of factor Xa as I recalled it in 2001.*

Counsel: *....What were you doing at the priority date in 2001?*

Dr Young: *...I was working in GSK,* [on] *the factor Xa programme. I joined the programme in...January 2000....I worked in that programme between January 2000 and towards the end of 2005....during which time we delivered two candidates....*

Counsel: *Can we now return to the preparation of your evidence?*

Dr Young: *Yes....*[T]*he first things I did was I reviewed WO131 and I prepared the report on the state of factor Xa in 2001, what people were doing and what they understood. And then gradually, I think the next thing was sharing common general knowledge.*

Counsel: *....If you go back to your first statement....paragraph 53...is where you summarise where the work had got to by September 2001 on small molecule factor Xa inhibitors....Where did this material in your report come from?*

Dr Young: ...[F]*rom my own experience and my own recollection of the important things at the time. And then subsequently this was reinforced when I started to read the papers that were handed to me. So, do we need to clarify that at this point? So, I didn't do a search to deal with this, Matthew Shade shared with me a number of papers and said to me, 'Do you recognise any of these papers?' To which my answer was yes. And he said that these were documents that had been used, representative of the common general knowledge in London. I then started reading those and then I was intertwining that in with the developing report that you see here.*

Counsel: ...[W]*here did the – you mention a number of molecules...significant inhibitors, starting at page 20 of the statement, which runs through to Example 6...on page 23....and 24. Where did those come from? How did you identify them?*

Dr Young: *So, I was asked to give almost a state of the union address as things were in 2001 from my recollection and then to reinforce it from what we could find in the knowledge. And DPC-423 was a no-brainer. I remember the shock waves it sent through our team and the reaction of our then programme leader when he saw the compound, it was so many picomolar and they were a hundredfold more potent than ours....I probably explained a little about Example 48, where and why I chose that compound. When these compounds came out, we did synthesise a few of them in our own programme with benchmarks, and we tried some of their motifs in our molecules....Fidexaban was an interesting compound, it was in many of the reviews....*[W]*ith the other compounds, again, I used my recollection and I was trying to illustrate how there was some change in modulating basicity and even getting towards a more neutral compound. But other than in the Lilly series, where there were a couple of examples of neutral molecules there, there weren't many compounds that were uncharged....I thought if I put Fidexaban in that will help the Court to understand what I'm talking about and it's not meant to assign any particular thing to it. So, that came from the searching I was doing....*[T]*he other ones are these examples where we've got just different bits of basicity. And they are spoken about in the reviews and there are comments as to which direction these things are going in. We have got compounds that have got either reasonably potent, they've got good anticoagulant activity, they've got the RPR 2443, that had good bioavailability. So, I presume you've heard from other experts what that means, you can take a pill and it will get to your systemic circulation. So, if you're not bioavailable you can't get a drug....*

Counsel: *Can I just pick up one thing...? ....You said that Matthew Shade gave you some papers....*[C]*ould you...tell us whether the papers listed* [at para.5 of the second witness statement] *there with* [sic – 'were?] *the ones that he gave you?*

Dr Young: *Yes.*

Counsel: *So, you've done that review. What happened next?*

Dr Young: ...[T]*he manuscript was reviewed. And I think it* [was at that] *point*

I was...introduced to application WO652.

Counsel: *Had you seen or heard of it before then?*

Dr Young: *...I was certainly aware of the compound. But Matthew said to me from the very outset... 'look it will take you about five milliseconds to understand where we're going with this, but please put that out of your mind. I want to take you through this stepwise.' So, that's why I didn't see 652 for maybe a week or two into discussions and I was spending quite a few hours on preparing reports and reviewing papers....*[B]*ut, you know, it didn't take me long to work this out, I could see where it was going.*

Counsel: ...[W]*hat happened once you'd been sent 652?*

Dr Young: *I was asked to review certain parts of that that became the basis for various paragraphs in my report. So, we went through embodiment-by-embodiment to see where I could use the chemistry side. Leading towards the part where the statement is in there about would the skilled person be interested to test any compound?*

[b. Embodiment 8; Figures 17-19]

Counsel: *Did you look at Embodiment 8?*

Dr Young: ....[Y]*es.*

Counsel: *What happened in relation to Embodiment 8?*

Dr Young: *That was very clear to me that that was an important part of the patent. It was very clear the patent was written in two parts, there are some distinct features of the molecules in the two parts of the patent and going through to Embodiment 8, it was quite clear what was of most interest to the applicants in terms of what they were doing. And as we'll get to as well at some point, the amount of compound they were making in many of these examples.*

Counsel: *In relation to Embodiment 8, it...is expressed in terms of a series of compound names....Were you asked anything about them initially?*

Dr Young: *Yes....*[A]*s part of probably in one of my interview processes, I was asked to take a name and produce a structure from it.*

Counsel: ...[W]*ere you able do that?*

Dr Young: *Yes.*

Counsel: ...[O]*nce you had done that, were you sent any further materials?*

Dr Young: *I was eventually sent a set of 110 structures as used in the London case.* [Same handed up]....

Counsel: *Is that a copy of what you were sent?*

Dr Young: *Yes.*

Counsel: *.... How were your statements written? Did you write them or were they written for you?*

Dr Young: *It was a combination of notes taken by Matthew in our conversations that I heavily edited after they were sent back to me, and there were elements that were lifted, as acknowledged, straight from the...London common general knowledge...*[T]*here were also...some quotes from some of the publications that I found particularly helpful in illustrating some...points.*

Counsel: *Who had editorial control?*

Dr Young: *Me.*

Counsel: ...[I]*s the statement in your own words or someone else's..?*

Dr Young: ...[M]*y words.*

Counsel: *Who prepared Figures 17, 18 and 19? Did you do that or did someone else do that for you?*

Dr Young: *I did it myself....*

[c. Work Method]

Counsel: ...[W]*hen you were doing this work, how did you approach it? Did you do anything out of the ordinary or unusual in relation to your normal working methods?*

Dr Young: *No, it's the expertise I developed during my time in the factor Xa programme to understanding as much of structural activity relationship....*

[d. Betz, Lipinski, and Zhu and Scarborough]

Dr Young: *So, if we look...*[at] *page 1010 of the* [Betz] *paper....he's recognising there are no biological data, but he's making opinions and he's noting what they were interested in in their patent. And if you look at the first three words on the top of the right-hand column, he's describing which five membered heterocycles or bridged heterocycles are most frequently used. So, quite clearly what Betz is doing when he is giving his opinion on this patent is he's doing a frequency analysis.*

Counsel: *And is that...similar to what you did on 652 or different…*?

Dr Young: *It's no different. And...furthermore, can we go to Lipinski?* ....[P]age 321 [p. 7 of the paper] *is the right page, Judge....So, we have the background and...we've talked lots about what Lipinski may or may not be. And what is particularly important in this passage...at the bottom of page 321*[p. 7 of the paper]...*what he's saying, what his target audience was, he wanted to put a message that medicinal chemists could clearly and easily understand. And if you read from just below the middle*...[he]*says: 'Keeping in mind our target audience of organic chemists...' who become medicinal chemists* '*..we wanted to focus on the chemists very strong pattern recognition and chemical structure recognition skills.*' So, [that is] *further evidence of why and how you would do this pattern recognition. You would do it subconsciously....*[T]*his was just using a quantitative way where you can put numbers on things to show trends, plot graphs to show things. I'm adding structures to these and colouring them as the tools were starting to become available at this time. It would help you to interpret and you could see through data, you could see patterns. Not only could you plot a graph, but you could put different colours, different shapes and it would enable you to identify different features. And these were the exact things that I have in my frequency analyses.*

Counsel: ....[Y]*ou will no doubt recall that I had a discussion with Dr. Edwards about the depiction of molecule 46 in the Zhu and Scarborough 2000 review....Dr. Edwards pointed out that it was missing a bond?*

Dr Young: *Yes....I believe Dr. Edwards is right. It's an error....*

3. Frequency Analysis; Synthesis

1099. As can be seen in the last few exchanges quoted above counsel for BMS and Dr Young had by now touched upon the issue of frequency analysis which they both proceeded to consider in further detail, as well as the issue of synthesis. At this juncture the following exchange occurred between them:

[a. Frequency Analysis]

Counsel: *I'd like to ask you to discuss the analysis that you did of the...652 application...in particular the frequency analysis and how you went about it. Now, first of all, when you look at a document like....*[the 652 application]*...can you explain...how you'd go about analysing or examining it...to find out what's in it? ...*

Dr Young: *You do judge a book by its cover here. You look at the front page and you see what's going on. Am I interested to open up this vast document? And, you know, you will see the title, you would see lactam-containing compounds and derivatives thereof as factor Xa inhibitors. Then, it will arrive within the skilled team, it may not just have been me at GSK at the time doing it, we would have had lots of alerts telling us when new patterns were coming out. You had to be on top of contemporary literature to stay alive, because it could ruin what you were doing. You would recognise the company, you would recognise probably some of the names and you'd think hang on, we know these people, you know, we've seen what work they've done before, where they're going now. So, you know, we've made some associations with the people and ultimately with structures that we recognise. So, the first thing I'd be interested in is does this impact the work I'm doing? You know, you would just straightaway look through is there anything in here that would generically cover what we have in our structures? And when you've done that, you'll start to think, well, what are they doing here? What are they using most often? And could that be of use to us? Could we incorporate that into a molecule? Remember we've got this hybrid molecule of core P_1, P_4 can we re-engineer our molecule it take advantage of some of their features and can we learn from that? Then finally, we might think, well, have they got something really interesting here? And is it worth making this in profile? And then you would have to go on a detective trail potentially to try and understand what the most likely thing was.*

Counsel: ...[W]*hen you're looking at the work that's described, how do you go about analysing it? What do you look for in relation to what they're telling you they've done? Are you interested in data?*

Dr Young: *I would be if there was some there. But I would be very surprised if anyone would go to the trouble of publishing a patent like this if it didn't have any data, of many kinds.*

Counsel: ...[W]*hat do you do when there's no data included in the document? How do you go about analysing a document like this?*

Dr Young: ...[T]*his is when you would look to see...what are they using most commonly and...are there any clues as to what the subject of this patent is? ....Again, I'm just doing here what I would have done when this thing came out. I would just flick through it...recognise a few things....*[Y]*ou'd recognise P_1 groups. You'd probably get a flavour from the title there may be some new groups in P_4. And, you...would...recognise from previous work a bit of a constraint on their core. So, those are the qualitative things you would do. But...you could then look at embodiments or the claims and you would just start drilling in* [to]*...what are they really interested in? Because yes, there's a huge molecule structure and billions of compounds aren't very many for a medicinal chemist....*[But *a chemist is not going to be frightened by this huge marker. So...you*

would look of ways of breaking it down...start reading it backwards and of course...look at the examples....

Counsel: *What were the interesting bits of this document?*

Dr Young: ...[T]*he way I was taken through it was to go through it embodiment-by-embodiment and... you could quickly get to the meat of the document....*

Counsel: *If you go to page 67 of the document...we get to Embodiment 7....*[a]*nd then to Embodiment 8....*[a]*nd I believe you've prepared a presentational aid to explain how you analysed these?* [Same handed up]....*It might be an idea...if you tell the judge about the International Union of Pure and Applied Chemistry* [IUPAC]*, so he knows where you're coming from.*

[Dr Young then explained the essence of IUPAC naming and how IUPAC names can be used to aid in identifying patterns in chemicals, continuing as follows:]

.

Dr Young: *....So, it's ways that you can use the naming conventions and the numbering to understand the frequency without recourse to structures, or if you wanted to, I think hopefully I've shown you here, how you could produce structures from what's written….*

Judge: *And if the patent turned up on your desk back in 2001, that's what you'd start doing, is it, taking things apart like that?*

Dr Young: *Yes, you would just look at, you know, what are they interested in? You may not have to go to the level that we're going to get a pattern. You know, you just see a whole page of methoxyphenyls, or nearly a whole page of methoxyphenyls. And, you know, the patent is telling us, in that distal group, that it's all about lactams.*

Judge: *And I know you're probably dumbing it down for me, but that would kind of jump out to the skilled person, is it?*

Dr Young: *I think so. Well, can you not see it? You know, it's word, it's recognition. And hopefully I'll demonstrate to you it's not too difficult.*

Counsel: *And can you see the core bicyclic ring structure in each name?*

Dr Young: *Yes….*

Counsel: ....[C]*an you give the judge an idea of how long this sort of exercise took you?*

Dr Young: *Well, we've gone through a couple of pages here and we're down to however many examples that is. You know, a couple of hours, max. And...you may take a little while just setting out your ground rules and recognising the different ones and...there will be some that will be a little bit different when they've got a variation on the lactam or a variation on the P_1. But...we've seen...which of those things we can recognise and see very quickly based on those numbers that have given us that signpost to work to.*

Counsel: *If we go back to your first statement...I'd just like to ask you to go through the reasons you give in paragraph 77* [for identifying Compound 18]....[D]*id the analytical work that you've done on Embodiment 8 and the synthesised examples which you set out in figures 17 and 18 feed into this?*

Dr Young: Yes....[T]*he structure is recognisable in part A. Part B, we're talking about the para-methoxyphenyl, so that repeated ring we see in...more than half the structures. And you could actually start looking at the variations that they do for these things together. So, we can see that that is coming together. We then need to move to*

point C, where you can recognise that we have this cyclisation or rigidification of the core, confirmed for several reasons. And you can see that from the analysis. And Embodiment 7 is showing you that it's a rigidified core. The skilled person would fully understand that and they will recognise its genesis from DPC423....[I]*t's like going back through the lineage of a horse you're putting your money on...*[I]*f you go back to its grandparents, its sire, its dad, you can see where the little bits come from; it's almost in the genetics of what's coming together. Then part D is the lactam. And it's said elsewhere in the report that the skilled person would very quickly recognise that, right back to embodiment 1, every molecule defined in there is a lactam, or sultams....There are some with slightly different connectivity in terms of nitrogens, but they've all got that recognisable structure with the nitrogen next to the carbonyl for the ring. And every single example and named embodiment in here contains a lactam. And that's the title of the patent. I should make it clear that, of course, the core part is a lactam as well. It's in my report. But just to recognise that....*

Counsel: *....You've given two more reasons over the page.*

Dr Young: *Yes...I guess we're back to the embodiment. And again, that's the thing in colour on the handout that we handed in. And you can see what people are using many times, they're most interested in those two particular carboxamides. And when you go through it, you can see in the patterns that many of the things in that embodiment have just got one change. So they have changed R_3, the jockey, they've looked at the P_4 that you recognise with a couple of variations on R_3 and they've varied P_1. So, they're looking at things that they're familiar with. But you really see which ones they are using most often.*

Counsel: *Then finally, point F?*

Dr Young: *So, this is the scale. And that stands out. I actually haven't got the book with the Norwegian proceedings in, but there is a graph I produced in that...where there's a huge statistical significance in the difference between that 3g and everything else that was made in the application. And that will attract the skilled medicinal chemist. It's one of the first things that...most medicinal chemists... will look for is how much of this compound is there, how interested in that compound.*

[b. Synthesis]

I. General

Judge: *I think Dr Edwards said 3g was pretty much kind of standard....*

Dr Young: ...[T]*here's been a lot of talk about the practices – and some of this is in my report – in 2001, about how much information you can get on how much compound. And you will see that the vast majority of compounds, where they've reported how much they've made, they've made as little as 1, 2, 3mgs or up to 20mgs. There are a few, there's about four, I think it is, that have got about 500. They may be interesting as well. To make 3g is quite an effort. And I don't know, at some point, if we'll go through the synthesis, but it's quite a complex synthesis and it's a very low yielding synthesis to get to that 3g. So, those combination of things is telling you how*

interested they might be. So, sorry, if we go back to those 3mgs, if you've got that much, you could get your primary data, you could get your factor Xa data, you could get your selectivity data, you could get some physicochemical properties on it, you could get some in vitro DMPK – you may have heard the experts talking about doing turnover, permeability and these kind of things. You could get enough information on that to know would you want to do any more....

II. Difficulty of Synthesis of Compound 18

Counsel: *You've mentioned the difficulty of synthesis of compound 18.*

Dr Young: *Yes.*

Counsel: *You've done, if I can put it like this, a visual illustration of that. It's in the last tab of the cross-examination materials for Dr Edwards, tab 5....*[a]*nd I think you mentioned, a few minutes ago, your view of that synthesis. Is there anything in particular you would like to draw the judge's attention to in that diagram?*

Dr Young: [H]*opefully, Judge, this can be a little bit helpful to you. Again, there's some colour coding....intended to show where the different little bits come from.... I used to always tell my friends at university* [that] *chemistry is cooker*[y] *in its purest form – you know, I just go into the lab and do a recipe and see what I get. And here you're trying to make a drug rather than a cupcake. And it's quite complex and there's a myriad of different ways that you can put these things together. And what this is attempting to show is the decisions that you would need to make and how you would put apixaban together.*

So, we've got these six different steps you need to do to put apixaban together. And at different steps, you will fix certain parts of the molecule. And you've made that decision earlier or later as to what to put together....And our part A product is recognisably a lactam...[a]nd this is them on a huge scale. They've made 51g of this, so they're pretty interested in it. Although where they go from there gets rather difficult.

So, part B, they now have to activate this to put a group on that will allow them to couple on the bottom part of the diagram. If you actually read through the synthesis, they talk about doing this on 85g of the part A product. So, they've clearly done this multiple times. And of course, this particular product, if you go through the application, and probably some of the other applications, you will see that they could be sent in different directions and you can fix that fused ring in different ways.

And this is what you're doing, if I may, along the bottom. So, if we can start bottom left with the green compound, there's quite an unusual reaction, called the Japp-Klingemann Reaction, which is quite a high-yielding reaction and it has quite an unusual reaction....But it's doable and...reproducible, so you can make this part C product. And you can combine this part C with part B to make part D, albeit [that] *there's a rather poor yield. And you can see that they've done this on a very small amount in the publication.*

So, clearly, when you go to the right-hand side, where you are doing part E and part F, they've either scaled this or they've outsourced it. And, you know, scaling up the chemistry is difficult. This reaction is a condensation, it will produce an acid, so it

will -- or an acid-based reaction; the chlorine will come out and that will give you an exotherm. So, these things are notoriously tricky to scale up. And there's almost a rule of thumb that when you do a reaction, you might get 100mgs, you might scale up to 300, but you have to go you [sic?] *incrementally before you just do it on 50g, which they may not have done.*

And equally, using the technologies of the day – we've talked about combinatorial chemistry – it would've been entirely feasible to get a reactor with 100 wells in it and done that reaction a hundred times in parallel. So, you know, the technology was there to do that. It could've been outsourced.

But then you've got your part D product. And we've got, in green here we've got the P_1 fix, our para-methoxyphenyl, you've got the 'O' with the little bit coming off the phenyl group....We can decide where to take this molecule, based on what lactam we've put in to replace the iodine, which is the 'I' at the bottom left of the molecule. And you can see here we're using the valerolactam, which is the recognisable one that we've seen in previous discussions. And this isn't a great yield either. But this is a step where you could put a great number of variations in that synthesis.

So, if you have a team of chemists and you can see through the application – and you could use some of this to make some of the compounds in WO131 as well, so you would have bulks, bottles of these intermediates and you would decide who to do with this. And it comes down to the story I was telling you earlier: Do you make, you know, small amounts of 20 compounds to get more information or do you commit it to make quite a lot of one of them? So, if you're committing...to make just one compound, I think you're pretty interested in that compound I think is what it's telling me. And again, then you fix, in the last, the aminolysis, to finally get your grammes of product.

4. The Skilled Person

1100. When counsel for BMS put it to Dr Young that it had been suggested that the analysis he had done and the observations he had made were ones that would not have occurred to the ordinary person skilled in the art in 2001 reading the 652 application, Dr Young did not agree. When asked why he did not agree the following exchange occurred between himself and counsel for BMS:

Dr Young: *Well...straightaway you can see the amount being made of the final compound. The skilled person would also have realised what other things could've been done from other positions in that compound. So, all of these things are adding together to point in the direction of something that they're particularly interested in. Why else...would you do it? Especially with the other information in the patent.*

Counsel: ...[W]*hen you look at the list of observations that you've made in paragraph 77 as a whole, are there any of those observations that, in your view, would not have occurred to the ordinary person skilled in the art looking at this document? And if so, why?*

Dr Young: *I don't think so....I believe I've just set out the simple logic and the understanding of what I can read from the patent to see where these people have gone.*

Counsel: *Any of these things difficult for a medicinal chemist to identify from the text in the specification?*

Dr Young: *No. I believe I've shown you what you can do to get through to the structures and the analysis of what is in the patent. The skilled chemist would recognise the intermediates. And in the same way we've worked out the structures, you could work out what some of these intermediates were from their names and just the chemistry that's there. And you've also got the names of the final compounds. And there's a lot of ways of getting your password together to arrive at your answer.*

Counsel: *Do you need to draw out all the structures of Embodiment 8 in the worked examples in order to do this analysis* [the frequency analysis]? ....

Dr Young: *....No, as we've seen earlier on, you don't actually have to draw them out, you can use your knowledge and look at the names and what they're telling you. It's all using this very rigorous IUPAC system. It's entirely logical and very rules-driven.*

5. WO131

1101. Counsel turned next to consider WO131. He did this initially by reference to Figure 19 in Dr Young's first statement, asking Dr Young to explain briefly what he had found from WO131 by reference to Figure 19. To this, Dr Young responded as follows:

"*I've approached this, breaking the molecule down into the same recognisable parts as we've described before. We've noted the title of the application, its bicyclic structures. And you can see from the top bit where I've talked about the core, all of these compounds are recognisably bicyclic structures. And you can see the frequency of what they're using of these particular structures. And this is what Betz was recognising that we discussed earlier. You can see I've done a similar analysis of the R_3 group. You can see which direction of travel, what they're able to make in this particular one. And this pattern isn't teaching us very much about making the carboxamide that we've seen in WO652. We come around clockwise and we look at the P_1 group and you can see that we have lots of aminobenzisoxazoles. There's quite a few paramethoxyphenyls, they clearly have some interest in that. And they have some variants of the aminomethyl, which was the group that was found in DPC423. So, you know, recognisable SAR to someone who is skilled in seeing the different groups in there. We then come to, if I may go to the top left, the P_4 proximal ring. This is the one that's got the 'F' above it, which is – many of these are substituted for fluorine, as was done in DPC423. And you can see that all of these compounds, all 109, are either the phenyl ring or they incorporate in the fluorine into that as well. But the key point of difference in WO131 is where you come to...[the] distal ring...in the bottom left of the molecule. And 95 of those are just plain aromatic phenyl ring. There are 12 variants that are imidazoles, which is a small heterocycle with two nitrogens knocked together with a pyrazole, that the skilled person would recognise. And then there are a couple of examples where they've probably looked at an intermediate, which is the bromo compound they would've made some of these from. And they've looked at dimethylamine there – it's probably not clear, but it's the exception of the rule in where they're going. But importantly, on all of these groups, if you look back to the structure, you'll see I've written R_2. And you will see there's a variety of exemplars in the synthesis. And we have all of these basic groups where we've got, at the bottom we've got 69 that have CH_2, N, R_1, R_2. So, they're all basic, they're all quite bulky groups, the properties of these may not be great – I've spoken in my report about the issues with the basic compounds and oral bioavailability etc....So the bulk of it are like that. And they've got a few examples as well, almost the balance, where they have the SO_2 methyl, so it's a sulfone, or the primary sulphonamide, which is the recognisable groups that we've seen in the DPC423, the example in the common general knowledge.*

So, we can see that's the direction that this is going. And absolutely nothing in here in the examples is a lactam. You know, it is generically covered in some of the highest embodiments, but it is one of the very large number of options and I wouldn't hide that".

1102. Counsel led Dr Young next to para.91 at the bottom of p.36 of Dr Young's first witness statement (where Dr Young sets out the choices that would have to be made to go from WO131 to apixaban) and asked Dr Young to summarise what he thought the likelihood of making those choices was *without* the teaching of 652. To this, Dr Young responded as follows:

"*So, what we have is the core. And WO131 is showing you a number of different cores that work, as recognised, as discussed earlier by Betz – that's part A....Then we go across and if you look at my frequency analysis, 39 of the 109 examples in there are the methoxyphenyl. It's one of several known groups to put into the P_1 pocket. You know, it was just getting this away from... the very heavily basic groups that were used in P_1 and it was one of the key things to get things over the line. So, it's one of several choices there. We then have to look at what is our best group to put at the R_3 position. So, we've got this thing together, it's almost like we've made our horse, we know what our bottom is and we get to apixaban and we know the methoxy, we know the core. That top bit is almost, it's like choosing me over somebody else in the courtroom to ride it in the Derby; you know...you want a ...*[small] *fit jockey on there. And in a way, that's what carboxamide is doing. And it is against the run of play in 131 to be chosen as the core. Of course, the keyest thing is that distal part, the lactam. There is nothing in 131 that gets you towards that lactam, which is, as we discussed before, it's this plausible system. And actually, importantly ... but we were talking about fluorine and getting the orientation of rings; one of the things that sulfone, the amide or even the lactam oxygen would do is, when you have two rings, they will tend to want to sit like this in congregation* [Indicating]....*But if you put a big lump of a group on there, it will...induce a twist into the structure, and that will freeze you out in the preferred confirmation of that molecule to get the best cwtching in you*[r] *pockets, you've got the overall interactions. You can go back to the one of the Shannon and Wexler papers where they talk about how they discovered the biaryl group; it came from an old thrombin programme. And they noticed, when they were putting groups in that position, they were improving the potency. And you just want something that's small in there, benign there – probably a fluorine would be too small in this position – just to get what you need in your final molecule.*"

6. Maignan and Mikol

1103. Counsel for BMS next brought Dr Young to the Maignan and Mikol article and asked Dr Young to give his view of the significance of that article in relation to what the state of the art was at the priority date. To this, Dr Young responded as follows:

"[T]*his article was one...of sort of a special issue of current topics of medicinal chemistry...*[I]*t was an early volume of a new journal. And there were quite a few of the big players had reviews in this paper....And what Maignan and Mikol have done very eloquently is they've talked about the state of the art about structural things and understanding how your compounds apply. And, you know, I'll be the first to admit it's not a guarantee how things bind, but it's one hell of a hypothesis-maker. If you've got an idea of how things are going, you can use that to see, you know, can we put something bigger to cwtch in there, can we see a way of making a hydrogen bond where you might get specificity into your compound? If you get complementary hydrogen, it's a good thing and it will tend to make your compound more selective. So, we can see the blueprint is in here for how we construct our molecules ....*[T]*here's a lot of knowledge in here to help you on your way. A lot of it is docking. Some of it is*

using surrogate proteases. So, a trypsin-like serine protease, it means it's like the digestive enzyme trypsin. And it was recognised as this basic group P_1, which we find a way of picking up that pocket, because it features in it. It's then the other pockets where you get the selectivity. And it inelegantly [*sic* – 'elegantly'?] *sets this out and it makes the comparisons with all the knowledge of what likely outcomes are. It talks about how you could plausibly get selectivity in your compounds and it gives examples of where people, how they've achieved it and reviews where the issues are and it talks about similarities and differences with the proteins. At this point, people were starting to get better at solving the factor Xa structure. We were getting pretty close at GSK and ultimately we did get these quite routinely. But other companies were doing the same and, you know, there are other sort of contemporaneous papers where people are starting to report more and more factor Xa structures....I wouldn't say to you that it's absolute gospel, but it ain't half useful to help you generate your hypotheses, understand the direction of travel. You do see some of the places where perhaps some of them can flip binding modes. And some of the reviews talk about this, you know, this way that you can do it and you can plausibly put them either way around and it doesn't actually matter, because it will still bind. And, you know, this is very eloquently set out in this paper.*"

7. Zhu and Scarborough

1104. Counsel for BMS asked Dr Young to give a similar sense of Zhu and Scarborough (2000), *i.e.* to give his view of the significance of that article, in particular the said commentary, in relation to what the state of the art was at the priority date. To this, Dr Young responded as follows:

"[T]*he first paragraph, 'Drug Design Perspective and Issues', is probably a rather more eloquent summary of where things were in terms of structure than I've just given you. But...it's showing you the basis of what people could do, what people were understanding, the developments that we were making....[I]n particular, when I re-read this chapter for the first time in 20 years...when you looked at the development issue...I describe this as prescient in my summary. Because, you know, what they're saying there* [are] *the exact things that people were doing and the compromises that you need to make in drug discovery. I'm sure you're familiar with the term 'Goldilocks zone' – 'it's not too hot, not too cold, it's just right'. Well, drug discovery is like having 15 'Goldilocks zones' interlocking; if you get it right for one thing, you've got it wrong with another. And it's a discipline all about compromises. You know, he talks in here that if your lipophilicity is too low, you will tend to be poorly permeable, but you will be soluble....And most of the drug discovery is this, the idea of partitioning these things....But he talks about the issues that you need to do to get this right. Again, he talks about, or they talk in here in detail, describing...the compromises you make there to get low protein binding, so more of your compound in a free form can go in and bind to factor Xa. So, that's what they're telling you here. And it's a very...informed and very educated summary about saying this is what needs to be done and this is where we are now, you know, which of these compromises will lead to drug substances.*"

C. Cross-Examination

1. The 652 Application

1105. Counsel for Teva began her cross-examination of Dr Young by putting a series of propositions to him concerning the 652 application.

I. Biological Data

Asked to confirm that there is no biological data in the patent application, Dr Young indicated that this is not so, that there are sections of data where they disclose that the compounds in this application are shown to be useful with an activity of less than 10 micromolar. Dr Young referred in this regard to the section of the application (at p.170) where it is stated that: "*Using the methodology described above, a number of the compounds of the present invention were found to exhibit K_is of less than 10 micromolar, thereby confirming the utility of the compounds of the present invention as effective factor Xa inhibitors.*" At this juncture the following exchange occurred between counsel for Teva and Dr Young:

Counsel:	*That's a statement, where do you see the data?*
Dr Young:	*It's a statement saying that they have active compounds.*
Counsel:	*Active in the amount of 10 micromolar?*
Dr Young:	*And more preferred ones are more active that* [*sic* – 'than'?] *that.*
Counsel:	*So, your evidence is that there's data in the patent application to the effect that 10 micromolar is active, is that right?*
Dr Young:	*I think we're splitting hairs on the use of language here. They clearly have made compounds and tested them....*

II. Compound Testing; Potency

Counsel:	[I]*s there any data in* [the] *patent application that tells you that any specific compound has been tested?*
Dr Young:	*No, there is no data point associated with any specific compound.*
Counsel:	*And there's no information in the patent application that any particular compound has a specific level of potency..? ....*
Dr Young:	*No, there is no association of a structure or a compound at any level.*

III. Selectivity

Counsel:	...[I]*s there any information in this patent application that tells you that any specific compound is selective against other serine proteases and trypsin-like serine proteases such as thrombin or otherwise?*
Dr Young:	*...I have to concur with you but all of the information is in here about how you can establish the selectivity of your compounds. And...I would find it very hard to countenance the fact that these people had not looked at some of this data....*

IV. Thrombin Inhibition

Counsel:	*I assume you agree that this patent application discloses that some compounds of the present invention were shown to inhibit thrombin, isn't that correct? ...*
Dr Young:	*Yes....*[T]*hey're suggesting that some of the compounds can inhibit the related trypsin-like serine protease thrombin....I've set out some comments about thrombin in my report, noting some similarities. And you will also see comments about the potential for dual inhibitors of thrombin and factor Xa that were of interest to the skilled team at the time....*
Counsel:	*There's no statement of any theory, rationale, reasoning for how the compounds encompassed by the application are said to inhibit factor Xa in the application itself*[?]*....I'm not talking about CGK, this is strictly talking about the application?*
Dr Young:	*My answer to that is the skilled person will read this, we know what*

the generic structure is, P_1, P_4 core, etc. The skilled person will recognise that and they'll recognise elements of that in structures in there that the skilled person could generate relatively easily...and they would make those connections.

2. The CGK Document

1106. Counsel turned next to a series of propositions concerning the agreed CGK document. Asked whether:

(i) (a) the structure of factor Xa, and (b) the S_1, S_4 and L-shaped core were in the common general knowledge, Dr Young indicated that this was so,

(ii) there were a number of inhibitors that were part of the common general knowledge, most notably DPC-423, Dr Young indicated that this was among many known,

(iii) it was known in the CGK that the S_4 pocket of factor Xa allowed for wide flexibility, Dr Young responded "*Yes, you could take that out from Zhu and Scarborough and Maignan and Mikol*",

(iv) it was well established in the CGK that when you make small changes to a molecule it can have unpredictable and significant effects, Dr Young responded that "*It is a fact but it's not always the case*".

(v) in the specific context of factor Xa there was a known risk of reversing or flipping between the S_1 pocket and S_4 pockets, Dr Young responded that "*There was the potential, as acknowledged from Maignan and Mikol and there was some disagreement between some publications in some of the work...Zhu and Scarborough in particular that were done. There is some extrapolation from some of the structures you would see in Maignan and Mikol from the work they did in bovine trypsin. But it doesn't matter. They bind*".

(vi) one knows they bind by testing them, Dr Young indicated that this was so,

(vii) without testing one cannot know what way it is going to bind because there is always that risk of flipping, Dr Young responded that "*Even with a crystal structure you could not be absolutely certain....*[but] *it probably doesn't matter, you know, crystallography is a very useful hypothesis maker and tester. It will help you and help you interpret the data in the observations that you see*",

(viii) "*it's an iterative process*" (I understand this to be a reference to the testing process), that you have to keep modifying and testing to see what the effects of the modifications are, Dr Young indicated that this was so,

(ix) as a basic matter, if one wants to do a test one needs to know the results of the test, Dr Young indicated that this was so, adding "*As I said before, I can't believe that they've gone through it this volume of work without having these data.*"

3. Medicinal Chemists

1107. Counsel for Teva turned next to certain propositions concerning medicinal chemists and literature searches.

1108. Asked whether medicinal chemists "*are usually what you would call general practitioners, much like barristers in Ireland, you won't necessarily know your target and when you come into it you have to then read extensively*", the following exchange occurred between Dr Young and counsel for Teva:

Dr Young: *...I think...everybody needs a little explanation here....*[I]*n 2001 the common way to get into the pharmaceutical industry – and it was a much bigger industry in those days – is you would come in as a*

pretty expert synthetic chemist....So, you come in as an organic chemist, and as you've seen from all the other witnesses, it's a black box and...we're skilled in that art. We know how to make molecules. We know how to change them. And very often....[y]*ou have to kind of assimilate some of what they're* ["*our colleagues, our pharmacokineticists, our pharmacologists*" are] *doing....*

Counsel: [So]*...generally you would be a general practitioner and you would have to then learn and read in when you come on to a new project....*

Dr Young: *But the principles of what you do are....transferrable....*

4. An Explosion of Factor Xa Writings and Patents?

1109. Counsel for Teva observed that from her review of the literature there was an explosion ("*and that's a commonly used word in the literature*") of writings and patents in relation to factor Xa around 2001, and asked Dr Young if that was his understanding also. At this juncture the following exchange occurred between Dr Young and counsel for Teva:

Dr Young: ....[T]*here were a lot of people in this area, it's a highly competitive area.*

Counsel: *And a huge amount of literature being generated, wasn't there?*

Dr Young: *A certain amount. Most of it probably in those days was in the patent literature. There were the reviews. There were some of the publications like DPC-423 that made waves....*

5. Selectivity, Potency, Testing

1110. Asked whether it was a correct summary of his view that "[T]*o identify a compound that might be promising you need to know about its in vitro potency in a chromogenic assay, its anticoagulation by measuring its prothrombin time and its selectivity against off-target proteins like the ones in the coagulation cascade*", Dr Young responded "*Not exactly*", at which point the following exchange occurred between Dr Young and counsel for Teva:

Dr Young: *So, you'll get your potency. I think I did write in one of my reports about using a fluorogenic assay as well. I remember at GSK we had to change the assay because the chromogenic wasn't sensitive enough. Everyone would set the assays up differently. It's always a balance between sensitivity and a signal. I'm not an expert in the pharmacology there but we did have to change. We almost – invariably if we had a reasonable level of potency we would go straight to the PT assay it was almost on the nod because that was the number that really mattered. I agree and disagree on selectivity. When you got into a series you kind of got a bit lazy that you kind of assumed that you tested a few, that you would keep that selectivity up. Then you would get bitten and you would go back and you would look at them....You wouldn't do everything all of the time. You've only got a finite number of people in the team. Every assay, every well, every experiment takes time and resources. We're pragmatists as a discipline in medicinal chemistry.*

Counsel: *You've just mentioned the question of selectivity and I think it's common case...that if you're dealing with a factor Xa inhibitor you do need to be careful to ensure that you're not also inhibiting other serine proteases; you need to test for selectivity...?*

Dr Young ...[A]*s outlined in my report, it is important here to be talking*

about the different kind of serine proteases. There are very many different serine proteases....[T]*heir common theme is there is a serine in the active. The serine is the tooth of the enzyme that goes in and actually forms a chemical bound and is hydrolysed. So, serine protease is a huge family. You then subclassify them by the architecture....*[W]*hat we're interested here are trypsin-like serine proteases which recognise this basic group, an arginine thing in* S_1 *and it's called the primary specificity pocket....It's called the primary specificity pocket for a reason. It has something to latch on to and that's what it will recognise. The other bits are just the extra bits that get the fine-tuning and that's why you can get selectivity between thrombin and factor Xa, etc....There's a lot of different answers to that question.*

Counsel: *But the overarching point is that you'd need to test and know about it, wouldn't you? ...*

Dr Young: ...[Y]*ou may do it* [testing] *late on, you may do it early*[,] *you at least want to benchmark your series.*

6. Dual Inhibitors, Specificity, and Selectivity

1111. Turning next to the prospect of dual inhibitors, counsel for Teva noted that in para.38 of his second witness statement Dr Young mentions the prospect of dual thrombin in factor Xa inhibitors and thrombin inhibition. (In fact, sometime around 2001 Dr Young in his own words "*discovered one by accident*". In para.38, Dr Young states, among other matters, that "[S]*ome of the alternative central scaffolds described in the examples of the Application could indeed have favoured thrombin inhibition by interaction with the S2 and S3 pockets of thrombin*"; counsel for Teva asked Dr Young "*to confirm that that just illustrates what you were saying is that it's important to know and test*". To this, Dr Young responded as follows:

"*Again, when do we talk now about specificity versus selectivity? So, what you get – let's focus on Embodiments 1 to 8, the line of travel there as the compound is getting more and more optimised it's cwtching...and we're starting to fit. We're starting to get polar groups in there and polar groups tend to engender specificity....This is the direction of travel that will get you that specificity. As we've talked as well, the architecture of thrombin versus factor Xa is quite different. You know, factor Xa has this box with three aromatic rings we talked about. Only two of them exist in thrombin but the architecture around it is very different and there are discrete* S_2 *and* S_3 *pockets that will bind. And if you read Maignan and Mikol he says that* S_2 *doesn't matter and it doesn't exist in Xa...And the next one is a bit indiscrete in factor Xa but in thrombin you would tend to go to those. In my experience, you know, you would see a set of structures and you could probably say that's likely to be factor Xa, that's likely to be thrombin and some of the others you will see them and they will flip round. There is a paper that I should draw attention to. I believe it's in...tab 2 of the bundle given to Dr. Edwards. ....So, they're recognising...how there could be utility in how you can change that selectivity.*"

7. Dr Young's Role Around the Priority Date

1112. Counsel for Teva proceeded next to consider Dr Young's role around the time of the priority date. To this end, the following exchange occurred between counsel and Dr Young:

Counsel: ...[A]*s I understand it, you were working in the area of factor Xa and prothrombin inhibitors from January 2000. I think you said you started right at the beginning of the millennium working in this field?*

Dr Young: *Yes.*
Counsel: *And went on to 2005. So, more of your experience in this field actually postdated the priority date, isn't that right, most of your relevant experience?*
Dr Young: ...[Y]*es....*
Counsel: *And I note in your CV...you don't mention any articles...prior to 2006. Is there a reason for that?*
Dr Young: *Simply because we hadn't got around to writing them up. I think you might see there are some patent applications that were published prior to that.*

8. Dr Young's Awareness of Apixaban

1113. Counsel for Teva turned next to consider Dr Young's prior awareness of apixaban. At this juncture the following exchange occurred between counsel and Dr Young:

Dr Young: [Y]*ou were aware of apixaban as a compound since about 2009 or 2010..?*
Dr Young: *Yes....*
Counsel: *So, apixaban is a compound you were well familiar with when you first became involved in these proceedings?*
Dr Young: *One of the things that I was deliberately told* [,] *was to forget everything I knew about compound 18 or apixaban....*
Counsel: *But you don't...mention in your witness statements that you were aware of the compound that we are referring to as apixaban before you came to do your work in this case?*
Dr Young: *I didn't explicitly state that. But I imagine there wouldn't be many medicinal chemists who weren't aware of apixaban.*
Counsel: *But you don't address it in your witness statement....*
Dr Young: *Well, that's a simple fact. I can't argue....*

9. Dr Young's Discharge of the Role of Witness

Counsel: *I gather from what you said yesterday...that it was sometime in February* [2022] *that you first got contacted by e-mail by Matthew from WilmerHale..to act in these proceedings..?*
Dr Young: *Yes....*
Counsel: *Are you aware that Dr Camp gave evidence for Bristol-Myers Squibb in early February 2002* [sic?- '2022'] *in England?*
Dr Young: *I am now...I...wasn't then....The first time I was aware of the UK trial was when I saw a post from somebody at Pinsent Masons, who I am on LinkedIn with, was talking about the outcome of the trial....*
Counsel: ....[W]*hen was this LinkedIn post...approximately...?*
Dr Young: *I don't know. April/May.*

10. Briefing Documents and Process

1114. Counsel turned next to the process whereby Dr Young was briefed and the documents he used. The following is an abridged but representative account of the exchanges between counsel and Dr Young in this regard (it goes without saying that I have heard, read, and considered the entirety of all the testimony given at the hearings):

Counsel: ...[I]*n your first witness statement you say you were briefed with...WO652...the patent application, and WO131...*[I]*n your*

second witness statement you list some additional articles that you'd also been in instructed with....But is that all you were given for the purpose of preparing your witness statement for these proceedings?

Dr Young: *...I was almost sort of drip fed into this. So, I was first asked to look at WO131 and discuss the common general knowledge. We also had discussions about my own publications in the area.*

Counsel: ...[Y]*our evidence is that the only documents you were given were the articles you identify in your witness statement and the three patent documents..?*

Dr Young: ...[Y]*es.*

Counsel: ...[W]*ere you given any other documentation..?*

Dr Young: *This (indicating)....But that wasn't immediately....*

Counsel: *....When were you given that?*

Dr Young: ...[I]*t would have been some point in March, because things moved fairly quickly....*

Counsel: *....So, were you put under time pressure when you first became engaged..?*

Dr Young: *No.*

Counsel: *Were you given any sense of there being urgency...when you were first approached..?*

Dr Young: *...I was under no pressure to do this....*

Counsel: *How long were you told you had to prepare your witness statement..?*

Dr Young: *I don't remember being given a timeline....*[I]*t was a little while in* [when]*...it was said to me, 'What we're putting together here will become your witness statement...'....*

Counsel: ...[W]*ho said that to you?*

Dr Young: *Matthew....*

Counsel: *So...he tells you that these are the bits we're going to use for your witness statement..?*

Dr Young: *Ultimately we framed this evidence for the witness statement....*

Counsel *'We framed it'? So yourself and Matthew together framed what was going to be in your witness statement?*

Dr Young: *I believe I said that's the way we did it yesterday. But in the end I have, you know, full editorial control....And I changed many things in it.*

Counsel: *....So...you were given the structures at some point in...March...?*

Dr Young: *Yes....*

Counsel: *Your first witness statement identified the three patent documents that you have been given as the documents you were briefed with?*

Dr Young: *Yeah.*

Counsel: *Your second witness statement then listed some articles, 12 articles that you said you had also been given...and nothing else...Were you given the patent at the same time as you were given the other documents?*

Dr Young: *No....*

Counsel: [W]*hen were you given the patent itself? ...*

Dr Young: *I honestly don't recall....*

Counsel: *At paragraph 16 of your witness statement you identify a list of journals....My understanding is the first three items are textbooks..?*

Dr Young: *They are...*[a]*nd I believe that I added Comprehensive Medicinal Chemistry and Burger's to this list....*

Counsel: *What do you mean..?*

Dr Young: *...I was given sources of CGK, but in my opinion Burger's Medicinal Chemistry and Comprehensive Medicinal Chemistry are rather better than Graham Patrick's textbook....*

Counsel: *If you could look at paragraph 5 of that witness statement* [second witness statement] *....you say... "As a preliminary point, I have been advised that I should clarify that, when preparing my Expert Report for the Swedish proceedings, I was provided with the documents identified in sub-paragraphs (A) to (J) and paragraph 6 below…."*

Dr Young: ....[W]*e were putting these for clarity, because we had seen the list of papers from Dr Edwards and we were just wishing to show that these things are a little more advanced than we were presented with from the other side. That would have been the reasoning for this.*

Counsel: ...[Y]*ou saw Dr. Edwards's list of journals and you wanted to supplement it..?*

Dr Young: ...[H]*is lists were relatively bare....*[W]*e believe that the common general knowledge had moved on a long way....*

Counsel: *Dr Young, I do need to just ask you about what's in paragraph 5 of your* [second] *witness statement....What you say...is that you've been advised...after you...put in your witness statement in these proceedings that you should clarify that you were provided with the documents listed below. Now, you said in answers that you wanted to be more clear because you'd seen Dr Edwards' witness statement in his reports and his journals and you didn't think they were sufficient. So, that's why you went to this list. Is that...correct? ....*

Dr Young: *I can't speak to the exact chronology. But when we saw that list...I was quite taken aback, saying...most of these are not related to what's going on and...if you've done a full search, you would have been aware of these documents.*

Counsel: *This list that you identify in paragraph 5 is a list that was given to you..?*

Dr Young: *Yes, it was a suggested list. And if you look at this list...I have added a few papers in there....*

Counsel: *You were given this list of documents to prepare your first witness statement. What Dr Edwards listed as literature in his witness statement has nothing to do with that, does it?*

Dr Young: *No.*

Counsel: *No. So, the answer you gave is actually just incorrect when you suggested that it was because of Dr Edwards's list that you needed to put this list forward?*

Dr Young: ...[W]*hat I'm doing here* [is stating]*...that I was provided with these documents when I prepared my evidence....It's just...*[for] *clarity...so there's no doubt about the situation.*

Counsel: *....Who advised you that you should clarify this?*

Dr Young: *It would have probably been in discussions with Matthew Shade...*[a]*nd...when I had the first discussions with Irish counsel.*

Counsel: *So, you were advised that this should be disclosed...were you advised that it should have been disclosed in your first witness statement?*

Dr Young: *No....*[T]*hey were just being clear that I wasn't asked to do my own literature search....*

Counsel: *The question I asked you earlier was whether you were aware that*

Dr Camp had given evidence in England at the start of February and you said you were unaware of the English proceedings [until]*...you saw a LinkedIn post in April or May....*[Y]*ou've now said in your witness statement that for the purpose of preparing your first witness statement – so that's in February or March – you were told that these were the documents that were used in relation to UK proceedings. So, is it still your evidence that you weren't aware of* [the] *UK proceedings?*

Dr Young: *...I was aware there was some litigation in the UK, as I've stated here....But I was not made aware of what the progression of these proceedings was....*

Counsel: [F]*rom the perspective of my client, what we were aware of from reviewing your witness statements was that you had been given three patent documents. That's all we were made aware of in respect of your first witness statement. In your second witness statement we were made aware that you were also given a list of journal articles that hadn't been disclosed when you made your first witness statement. It now appears from your evidence you were also given a list of journals. And that's just the facts as I understand them from your evidence today.*

11. The Drawn-Out List of Compounds and the Frequency Analysis

1115. Counsel for Teva brought Dr Young next to certain correspondence between the solicitors for the proceedings in which by letter of:

- 30th June 2023, Pinsent Masons (for Teva) seeks a list of all documents provided to all of BMS's witnesses for the purpose of preparing their reports,
- 4th July 2023, McCann FitzGerald (for BMS) indicates that (a) they are "*surprised by your request for a list of all documents provided to our client's witnesses in circumstances where that information is clearly discernible from the witness statements*", later stating that (b) "*Nevertheless, we have made inquiries to confirm that no other documents were provided to any of our client's witnesses for the preparation of witness statements in other jurisdictions and no such additional documents were provided save for one document which was provided to Professor Morrissey…*",
- 7th July 2023, Pinsent Masons seeks confirmation, for the avoidance of doubt, that no other documents were given and also requests the search terms for literature searches carried out,
- 9th July 2023, McCann FitzGerald indicates that "*The materials referred to by our client's experts did not come from a literature search. There is therefore no reciprocal information to be provided*",
- 10th July 2023, Pinsent Masons repeat the request for confirmation that no documents were provided,
- 24th July 2023, McCann FitzGerald issued a reply in which it was stated that

> "[I]*n addition to what has already been confirmed....BMS's coordinating solicitors, WilmerHale, have recalled that Dr Young was also provided with the enclosed document while he was preparing his statement in the Swedish proceedings. Dr Young will address this in his examination in chief*",

the said document being the document that Dr Young indicated himself to have been given sometime in March, being a lengthy document that lists out 110 synthesised examples and draws out the structures next to the names of the

compounds.

1116. The following exchange then occurred between counsel for Teva and Dr Young concerning the just-mentioned document and Dr Young's frequency analysis:

Counsel:	*So, that's a document that was given that we hadn't been aware of, until Monday evening.*
Dr Young:	*And I think, Judge, as I showed you yesterday the skilled medicinal chemist could produce this very easily....*
Counsel:	*...Do you have any memory of ever addressing this document before?*
Dr Young:	*....I don't....*
Counsel:	*Did you forget you'd been given this document?*
Dr Young:	*No....*[T]*his was the document as acknowledged in Oslo* [in which]*...I noticed the mistake....*
Counsel:	*So...you had this document when you were giving evidence in other jurisdictions?*
Dr Young:	*I think I've been explicit that I used this document to generate my frequency analysis.*
Counsel:	...[Y]*ou were never explicit about that. You never, in your witness statements, disclosed you were given structures by anybody....If I could just ask you perhaps to go to paragraph 64 of your first witness statement? ...Can you read that paragraph please?*
Dr Young:	*"Embodiment 8 then lists a series of 74 compounds that are said to be preferred"....And I hope as I...demonstrated yesterday, the skilled medicinal chemist could readily analyse the structures of the compounds based on their chemical names.*
Counsel:	*When you wrote this, you had the document that you now have in your hand that was given to you by WilmerHale, isn't that right?*
Dr Young:	*That is correct....*
Counsel:	*You don't say that you were given the drawn out structures.*
Dr Young:	*I agree, I haven't said that....Perhaps in the interests of time, it was realised it would make my life a little bit quicker than drawing them out –*
Counsel:	*Okay....At para.65 you...say... "The figure below sets out an analysis of the frequency of particular motifs..." You don't say there that you carried out the analysis..? ...*
Dr Young:	*No, but I've signed this as being my report....*[a]*nd I can assure you that I did do this analysis.*
Counsel:	*Look at paragraph 70 of your statement at page 29. You deal with Figure 18....*[Y]*ou don't say you did the work..?*
Dr Young:	*I don't explicitly say that....*[b]*ut I do believe it's self-evident that I did do this.*
Counsel:	*It's just a matter of terminology. If you look at paragraph 82 of your witness statement you say..."...I have carried out a frequency analysis..."*
Dr Young:	*Well, my understanding of that would be that I have carried out a frequency analysis and the similar fashion would be myself carrying out that frequency analysis.*
Counsel:	*You don't actually say you carried it out in a similar fashion to how you carried out the earlier ones....*

1117. At this point, counsel for Teva returned briefly to the issue of what documents Dr Young was given for the purpose of preparing these proceedings. Counsel then turned to the issue of literature searches, the following exchange occurring at this juncture between herself and Dr Young:

[I. General (incl. Dr Edwards's search)]

Counsel: *As I understand it, and you discussed yesterday, medicinal chemists...if you come to a new project you'll do a lot of literature searches to try and familiarise yourself with what's available in the field. Is that right? ....*

Dr Young: *A literature search. And, you know, you would go to conferences, you would talk to other people.*

Counsel: *And you wouldn't, I take it...read thousands of articles to familiarise yourself, you'd try and find a selection? ....*

Dr Young: *Yeah, you find what you would like to read. But we're curious people and you would be interested to read around things....*

Counsel: *...And we know...that you did no literature search...for these proceedings?*

Dr Young: *I did not do an explicit literature search. I was given the set of documents and I agreed that what was in there was very representative of what my knowledge was at the time. And indeed I remember several of those papers very well. And you remember the names, you remember the structures. But in the course of my preparation of my report, you can see, I did use SciFinder....*

Counsel: [In his witness statement, Dr Edwards] *identifies the documents he was briefed with for the purpose of preparing the proceedings....*[and] *he identifies how... "In order to place myself in the position of the skilled medicinal chemist in 2001 joining a factor Xa drug development team in 2001 I carried out a literature search." He identifies how this would be standard. He says in 6.40... "Accordingly, I used PubMed as a search tool for my literature searches. PubMed was widely available in 2001...". Was SciFinder widely available in 2001, Dr Young?*

Dr Young: *...SciFinder is part of the chemical abstract service, which is the place that you would always go to in chemistry. I first used SciFinder in 1996....Can I also say that I can honestly say I'd never used PubMed....before last year....And I don't believe PubMed would have been the first place a medicinal chemist –*

Counsel: *We'll come...to your criticisms of Dr Edwards in a moment....[I]n paragraph 6.40....*[h]*e said he used PubMed as a search tool. He said it was widely available in 2001 and a skilled team would have regularly used it....He ran a literature search. Then he describes the searches he conducted....He describes the date range and he identifies the articles that he reviewed....[T]hen he says over the page that from his review... "I identified certain recurring themes or topics which would have been considered the CGK." And then he goes on to identify his summary of the state of the field from his literature search and his review of the literature he identified. So, you accept that it's typical to do a literature search....but the kind of exercise he did, I take it, is typical of what a medicinal chemist would've done in 2001...?*

Dr Young: *If you were coming to this absolutely blind, yes. But if you were joining a skilled team....there would've been a wealth of*

information coming together there.

Counsel: *That's fine. And let's look at what actually happened with you....You were, we now know, given literature by WilmerHale and you were told 'This is the key literature', isn't that right?*

Dr Young: *No, the question I was asked is 'Is this set of papers representative of your understanding of what was happening at the time?' And...'If there's anything you'd like to add to it, please do'. But on my review of those publications, to me, it gave a reasonable understanding of what was there at the time.*

Counsel: *Did you enquire about who did the searches to find these articles?*

Dr Young: *No....*

Counsel: *Did you find out if the person who did the searches was a medicinal chemist?*

Dr Young: *Again, to me, you know, the outcome was a very reasonable set of papers describing the state of medicinal chemistry in factor Xa in 2001. Which is rather different to the set of papers that Dr. Edwards presented.*

Counsel: *Did you enquire about the parameters that were applied to conduct the searches?*

Dr Young: *Again, when you have a set of papers that are telling you a lot of very useful information, it's very strange when you see a rather narrower group of papers presented to you from another expert.*

Counsel: *You understand the obligation of independence of an expert witness, Dr. Young..?*

Dr Young: *Yes. And my independence is something I'm renowned for....*

Counsel: *But when you were given this literature and told that this was the literature to read, you didn't ask any questions –*

Counsel (BMS): *I'm sorry,* [Counsel for Teva] *keeps doing this. And I'm just going to...make the point. She keeps saying things which contradict what the witness has told her repeatedly. 'You were told that these were the things to read.' He has never said that. He's said the complete opposite every single time she's tried to put it to him....*

Counsel (Teva): ....(to Dr Young) [I]*s it your view that you were asked to look through these as the key reviews?*

Dr Young; *No, they were not put to me as the key reviews....*

[Counsel for Teva now turned to question Dr Young by reference to an English-language translation of the Norwegian proceedings, which translation was the work product of her solicitor, had not been verified and may or may not have been a correct translation.]

Counsel: *If you look at the evidence you gave to the Norwegian court. And subject to any verification of a formal transcript that may follow....*[t]*here's a line saying... "Can you explain why you've chosen these six particular compounds?" That's referring to a different point that I will be referring to. You say: "Okay. I was asked just to use my memory and look through some of the key reviews that I was asked to read." Was that your evidence in Norway, that they were the key reviews you were asked to read?*

Dr Young: *Again, as I tried to explain to the judge, my experience of reading through these reviews is the translation - you know, whether "key" was the word I used? I may or may not have used it....*

Counsel: ...[D]*id you have a lot of time then, when you were given the literature...by WilmerHale...to read it and consider it?*

Dr Young: *I had enough time to satisfy my own mind and produce the report*

that I did.

Counsel: *But you didn't do any other searches yourself?*

Dr Young: *As I said earlier, I was using SciFinder to generate some of the physical chemical data....*

Counsel: *....I'm just dealing with literature for now.*

Dr Young: *And as I was doing it, I was just...trying to remember some of the things and...making sure I could get my memory right and just checking on other things of exactly and when did they come out and other things that I remember*[ed]*, were they pertinent to this?*

[II. Report of Dr Camp]

1118. I understand that Dr Camp was the medicinal chemist who gave evidence in the English limb of these proceedings. Counsel for Teva now brought Dr Young to certain elements of Dr Camp's report and then posed certain questions by reference to Dr Young's report.

Counsel: *If you would please look at paragraph 6.8 of Dr. Camp's witness statement. And it might be helpful if you've got your own witness statement open at the same time, Dr. Young....So, your witness statement at page 6, paragraph 16 and Dr. Camp's witness statement at paragraph 6.8 on page 10. So, do you see that from D to H you list the relevant journals in your witness statement?*

Dr Young: *Yes.*

Counsel: *And do you see that in (a) to (e) Dr. Camp lists the journals he would expect the medicinal chemist to be familiar with?*

Dr Young: *I ...note that I've got one extra on there as well.*

Counsel: *You've one extra. But you've others in the same sequence..?*

Dr Young: ...[A]*t the time these were some of the widely read journals that the medicinal chemist would be using, so perhaps it's not a surprise they're the same.*

Counsel: *It's a coincidence. Very good. If you continue on with Dr. Camp's report, at 6.9 he says:*

> *"Before preparing this Report, I asked Hogan Lovells to carry out two literature searches to refresh and update my knowledge as to what the state of the art was in September 2001 and to reflect that my personal involvement in factor Xa research ended when I moved to Eli Lilly in 2000... I asked Hogan Lovells Science Unit to carry out the following searches."*

And he identifies the searches. At paragraph 6.10 he says... "The results of the two searches revealed a large number of papers. Where appropriate, I have provided references…"....He then identifies the additional papers and he identifies (a) to (d) there. Do you see that list of literature?

Dr Young: *Yes.*

Counsel: *Does that look familiar to you?*

Dr Young: *Yes.*

Counsel: *Why does that look familiar to you?*

Dr Young: *Because these are some of the papers that I was asked to review by WilmerHale....*

Counsel: *If you would go forward to paragraph 6.7[0] of Dr. Camp's report....And you see that list of publications? ....*[D]*o they look*

familiar to you?

Dr Young: *So, you know, as I was explaining yesterday, the one place that medicinal chemists will get the most information from in a competitive area is to go to any reviews of the patents, and indeed the patents themselves. So, rather than textbooks, rather than even journals, if you want to know what's really going on, it's not a surprise that these are here. And as I said, these were shared with me, I've been perfectly transparent about that. And, you know, if...I was aware of more...I would've added them. But, you know, we have a representation of the art as was in 2001 that I do remember quite well.*

Counsel: *....I just have to put to you that the 12 articles you list in your second witness statement....are exactly the same 12 articles that Dr. Camp identifies in his report. And he identifies how he found those articles. Do you accept that?*

Dr Young: *...I don't dispute that each of the papers listed in here are those I was asked to review by WilmerHale....*[T]*here are one or two other papers I've supplemented it with as well.*

Counsel: *And I think we already talked yesterday about how there was an explosion of literature on patents around this time in the factor Xa field, isn't that right?*

Dr Young: *I think if you read these reviews you would understand that, yes....*

Counsel: *You identify at paragraphs 5 and 6 of your* [second] *report a total of 12 articles....And I want to confirm, for your own information and just to avoid any confusion, Dr Camp, in his report, identifies four of those articles in paragraph 6.10; that's Leadley, Light, Maignan and Mikol and Ries. At paragraph 6.7 he identifies Al-Obeidi, Betz, Pauls and Ewing and there's a Zhu and Scarborough in 1999. At paragraph 6.36 he identifies the Leung article. At 6.58 he identifies the Rai article. At 6.84 he identifies the Pinto 2001 article. And at 6.87 he identifies the other Zhu and Scarborough. So, that's the 12 articles you identify there. It's just a fact. I don't think it should be in dispute, it's easily verified. But I think you've accepted that the articles you identify here were ones that were given to you?*

Dr Young: *...*[Y]*eah.*

Counsel: *And there are some additional articles in your report....But the point I wanted to make was just there is a complete overlap between the list of articles you rely on and the articles –*

Dr Young: *....*[Y]*ou're asking experts to give an opinion on an area. And we're being influenced by what we're reading in the articles. And despite the explosion of literature, there probably weren't so many review articles out there....*

[III. Dr Young's Criticism of Dr Edwards's Literature Search]

1119. Counsel for Teva turned next to Dr Young's criticisms of Dr Edwards' literature search, at which point the following exchanges occurred between counsel and Dr Young:

Counsel: *Why did you think it was appropriate to criticise Dr Edwards' literature search?*

Dr Young: *Because I believe the number of papers he was giving in his evidence were rather out of date and not pertinent to the discovery of factor Xa inhibitors.*

Counsel: *You didn't do a literature search yourself..?* [I find it an odd

proposition, if this was the proposition being advanced, that Dr Young *needed* to do a literature search before he could criticise Dr Edwards's literature search. I accept the proposition, if this was the proposition being advanced, that the criticism would likely have been better informed if Dr Young had undertaken a similar process].

Dr Young: *Don't forget I was very familiar with what was going on in this programme at the time and I could...have my own memory jogged by reading some of these reviews.*

Counsel: ...[O]*ne of the issues with your memory at the time is that your memories at the time spanned a period from 2000 to 2005..? You understand how critically important it is for you to know the cutoff point?*

Dr Young: *...I could look at the dates on those reviews. And they were...very representative of what was happening in the field at the time.*

Counsel: *You criticise Dr Edwards for not describing the parameters of his search. Is that a fair criticism?*

Dr Young: *Well...you know, he's done this search and...with all of these potential papers he could've found and many that he didn't. And I find...if you want to get a good feeling of where an area was, there were some of these other papers that* [I?] *would've added and* [which] *would've probably educated him in some of the aspects.*

Counsel: *You agree five of his articles are relevant...five of the 11 he identifies?*

Dr Young: ...[S]*ome of them are overlapping. And he has done a search from a source that will give you some of the relevant literature. But it's called PubMed...which is not the same as Chemical Abstract Service, run by the American Chemical Society, which will give you more of the information relevant to the medicinal chemist.*

Counsel: *...Dr Edwards...was cross-examined for half an hour in relation to his literature search....I have to put it to you that it's not fair or appropriate to criticise Dr* [Edwards]*...when you didn't do a literature search....*

Dr Young: *I accept that he's done a search. But my criticism is that…, the result of that search, you know, is rather limited. And...he should be looking at things that are in my report that would bring him a little bit more up to speed with what was happening at the time.*

Counsel: *But...you were given the literature in your report, you didn't do a literature search....*

Dr Young: *But I think we've established, Judge, that....I could easily have done such a search. I would remember many of the names there, I've referred to many of them in my publications. And I was told to be very careful of, you know, focusing on the period when the patent was....posted.*

13. The Compounds Identified By Dr Young

1120. Counsel for Teva turned next to consider the compounds identified by Dr Young. She recalled that in the agreed CGK document there is a discussion about the large number of potential inhibitors that were emerging in 2001, the word "*explosion*" having been used to describe the compounds as well as the literature. Dr Young took what seemed to me to be the more moderate stance "*that there was a lot of interest going on, yes.*" Asked whether (i) in trying to identify relevant compounds to use for his report, Dr Young used his recollection, Dr Young indicated that "*It was a combination of factors....It was my memory and my reading of publications, the annual reviews and the patent reviews etc*", (ii) he agreed that it was not being put forward that W0131 was in the

CGK, Dr Young responded that it is mentioned in Betz but that he believed it was not suggested that it was part of the CGK, though "*someone would have to advise me on the technicalities. It was presented to me as part of the case*", (iii) it was the case that he did not select it as one of the compounds of interest, Dr Young indicated that he had not "[b]*ecause I think, as you've read in my report, I would find it very difficult to select the particular compound in WO131*".

1121. Counsel for Teva then turned to consider what Dr Camp did with regard to the compounds he selected. She noted that Dr Camp:

(i) discusses the Daiichi compound (which Dr Young agreed was one of the first compounds that had demonstrable efficacy),
(ii) identifies RPR-120844 (which Dr Young believed was a compound that he also identifies in his report),
(iii) identifies another DuPont picomolar inhibitor (which Dr Young agreed he had not identified: "[T]*hat's one of the precursors to DPC423, which is lacking a fluorine and a methyl group*"),
(iv) identifies another compound, ZK-807834 (which Dr Young confirmed he also mentions in his report: "[T]*his was a compound that had demonstrable in vivo activity at the low dose and...it had oral bioavailability, as I pointed out in my report)*",
(v) identifies fidexapan (also identified by Dr Young),
(vi) moving on to the less basic structures, identifies a Rhône-Poulenc Rorer compound, RPR-208815 (which Dr Young indicated was not one that he had identified),
(vii) identifies compound 20855 (which Dr Young confirmed was not in his report: "*I've used some of the features of that in my report. But there are some quite important and distinct differences in the compounds in my report*"),
(viii) identifies DPC423 (which Dr Young confirmed was a compound that, to use counsel's terminology when putting her question had "*been identified across the board*"),
(ix) identifies an Astrazeneca compound, ZD-4927 (which Dr Young indicated was also in his report),
(x) identifies a compound from the Lilly series (Dr Young indicating that although he too identifies a Lilly compound "*the compound that I put forward is quite distinct from this one*").

1122. The following exchange then took place between counsel for Teva and Dr Young:

Counsel: [T]*he point I was going to put...is that four of the six compounds you identified from the very large number of available compounds are exactly the same as four of the ones that Dr Camp identified, and two of the others comes from the same series, the two that aren't identified.*
Dr Young: *...I'd have to refresh myself to be very exact, but I believe some of the ones that Dr Edwards put forward are very similar as well.*
Counsel: *There was an overlap with, I think, three of them; DPC423, I think he accepted fidexaban was also CGK but I think there were perhaps two overlapped with Dr Edwards....But you identified four identical compounds. And of the other two, they come from the same series that Dr Camp identified.*
Dr Young: *Well, we've got three of them at least that are, you know, you've got some unequivocal statements.*
Counsel: *Well, two, I think, yes.*
Dr Young: *So –*

Counsel: *And your evidence is that it's a coincidence –*

Counsel (BMS): *Will you stop interrupting him? He's trying to speak and you keep speaking over him. He's trying to explain something to you. Let him explain.*

Dr Young: *So, Judge, what I'm explaining is, as I hope I've set out in my statement, that the direction of travel goes from...that very basic 9065. It's got excitement which show that factor Xa works. We've got to compounds where you can start putting things together – we're using a Lego kit, if you like, we've discussed that previously. And we can see that people are exploring what you can do in S_1, in S_4. A number of different groups have been identified because of the use of combinatorial chemistry and the advantages that brought. We can see incremental changes in the basicity, we can see the direction of travel. And included in Lilly are some of those examples – why I included it – that some of them are non-basic. The one that's there probably has a mild amount of basicity and it's also got an acidic centre....But...is it surprising that three experts in here are producing, or recognising similar compounds, if not the identical ones, the key things to help you make your decision as to make your decision how things were moving? And especially with DPC423, we've got an explicit statement that I quoted in my report that it was described as...perhaps the most exciting compound in the field at the time....It was one that was less basic, it had oral bioavailability, it was highly potent....It also has an element that could be hydrolysed...to produce an aniline....So, these are all little increments that you're starting to put together and, you know, you're making thousands of compounds, literally tens of thousands between the companies. And we're now honing in as to why just a very few of them are being selected.... And I hope I'm using that direction of travel to show us where we are as regards all of that was going on at the time.*

Counsel: *....So, I take it from that that what you're saying...that the Lilly series was identified by you? You know, you say it was non-basic and a neutral binder. And that's what Dr Camp has identified also. But –*

Dr Young: *...I did not say that. I put the Lilly series in as an example of an area where they had a number of different combinations of compounds. And some of them had better anticoagulant activity than others, some were neutral, some were basic. The compound there has got a fairly acidic centre in it as well. So, we can see this combination of things that people are trying and you could start to address in tests, with data, how good your compound was.*

14. The Conclusions to be Drawn from the Compounds

1123. Counsel for Teva turned next to the kinds of conclusions that could be drawn arising from the identification of the compounds. At this juncture the following exchange occurred between counsel for Teva and Dr Young:

I. General

Counsel: *Turning...to...the kind of conclusions you could draw from the compounds. I think you've agreed...that you can hypothesise about the impact of structural changes....*[b]*ut you need to test to do more..?*

Dr Young: *Well, it's self-evident...that as you make compounds, you make and test hypotheses. So you will test them, yes....*

Counsel: ...[Y]*ou say apixaban has the core-P_1-core-P_4 structure that was common to known factor Xa inhibitors..?*

Dr Young: *Yes....*[T]*he skilled person would recognise the elements of that structure from elements of the common general knowledge, with the exception of the....lactam....*

Counsel: *But we're talking here about the structure of factor Xa and kind of known inhibitors..?*

Dr Young: *Yes.*

Counsel: *And you've just said, I think, that...this structure was known as part of the CGK at the priority date...?*

Dr Young: *No, I have not said that this structure was known at the priority date. I've seen compounds with recognisable elements leading towards this structure [that] were known at the priority date. That's a slightly different proposition.*

Counsel: *Very good. In the agreed CGK document there is discussion about the structure of known apixaban inhibitors....If you look at the bottom of paragraph 128, it talks about DX9065a, which is the Daiichi compound, adopting an L-shaped confirmation when bound, which the literature reports to be necessary to place the P_1 and P_4 groups in their respective binding pockets. So, that structure was known in the literature is the proposition I'm putting to you....*

Dr Young: *Yes, this structure was known in the literature, yes. And it's in my report.*

Counsel: *....Is the proposition you put in paragraph 70A reflected in the CGK?*

Dr Young: ...[M]*y proposition...isn't that...we're similar to 9065a....*[M]*y proposition is...that we've got a new assemblage of building blocks with our super duper winglet on the end that...the skilled person would understand, having read the common general knowledge with an open mind...was plausibly a factor Xa inhibitor.*

Counsel: *I think in fact the lactam,... you deal with that in paragraph D....I'm just focusing on paragraph A for now....*[P]*aragraph A talks about apixaban having the P_1-core-P_4 structure that was common to known factor Xa inhibitors....The question is just whether the...P_1-core-P_4 structure...was common and known in the agreed common general knowledge in 2001?*

Dr Young: *Yes.*

Counsel: *....And also you talk there about factor Xa inhibitors having neutral or weakly basic P_1 and P_4 groups being of particular interest. And I think you've already said...that that was also part of the literature and common general knowledge, that there was that move.*

Dr Young: ...[Y]*eah, at the time there were a number of inhibitors described. Remember...that at the bottom of P_1 we have this acidic group, that's point 189, that would bind to a basic group. It was dogma for a while that you would have to make that group. And we've seen the emergence of fluoroaryls involved, para-methoxyphenyl, dare I say. You go in there and it's like it's almost literally pick the pocket and get in there in a way that otherwise wouldn't happen, because there are particular features that you could literally pick. So, that's the direction of travel. Some people retain basicity. In S_4 it talks about the potential quadropole, it's spoken about in*

Maignan. But, you know, if you read the common general knowledge, if you could get to a neutral compound, it would be better. You know, we've spoken about bioavailability, the problems it can cause there. It's the neutral form of molecules that go through membranes or are absorbed from the gut. There are also things like cardiovascular toxicity, I believe, talked about in the report....[T]*hat really came to prominence in the early noughties, that people realised that this was a toxicity risk with many compounds. It was easy to put a basic centre into the compound to rescue your lipophilicity. You may get away with getting oral bioavailability, but you ran the risk of cardiovascular toxicity. So, these are all reasons of this direction of travel.*

Counsel: *...I think that's common general knowledge and not in dispute....The next limb of your paragraph 77 is that apixaban has a methoxyphenyl group in the P_1 position. And you say there that the methoxyphenyl substituents have been shown to bind in the S_1 pocket. And you refer [state?] in paragraph 48, which is referred to in that subparagraph [that] "The significance of this molecule and/or closely related examples in the series were noted in Maignan, Ries, Zhu 2000, Zhu 1999, Betz and Rai."*

II. Various Articles Considered

1124. Counsel turned next to a consideration of various of the just-mentioned articles with Dr Young. At this juncture the following exchanges occurred:

A. Maignan and Mikol

1125. Counsel for Teva drew Dr Young's attention to the section of this article (p. 167) where, in a paragraph about the neutral P_1 group it is noted that Lilly scientists had discovered a neutral P_1 group, the article then moving on to observe that "*A chlorophenyl [36] could also replace the methoxyphenyl with a 6-fold improvement in potency and about the same in vivo efficacy by intravenous administration as the benzamidine equivalent compound.*" Counsel then asked whether this text pointed to methoxyphenyl as the most interesting substituent in the P_1 pocket. The following exchange then occurred between Dr Young and counsel for Teva:

Dr Young: *I will concede...that if you're solely interested in potency then your statement is correct. However, I'm interested in making the drug, so I look beyond potency.*

Counsel: *You don't identify that in your witness statement. But we'll go on to one of the other articles.*

Dr Young: *I'm sorry, Judge, I do....There are numerous times in my statement where I talk about this.*

Counsel: *I'm looking specifically at paragraph 48, Dr Young. Sorry, I should've been more clear.*

Dr Young: *Well, I'm a bigger picture person.*

B. Betz

1126. Counsel for Teva brought Dr Young next to the Betz article (p.1013) where, in a consideration of compound 36 (which Dr Young agreed had a methoxyphenyl substituent, though with several other changes also), and a potency of 150 nanomolar, it states, amongst other matters that:

"*This new family of compounds, exemplified by compounds 36 and 37 are potential*

leads for the synthesis of orally bioavailable Factor Xa inhibitors, since amidine-containing molecules have undesired pharmacologic properties....SARs for derivatives of 36 indicated high potency, when the p-chlorophenyl group was replaced by p-methoxy phenyl."

1127. Having led Dr Young to this text, the following exchange then occurred:

Counsel:	...[A]*s I understand it, that's actually an error....There's no chlorophenyl in...number 36..?*
Dr Young:	*I believe what he's saying is he's coming to the opposite conclusion to Maignan and Mikol....I would have to go through the paper to check this - but he may be suggesting that the actual order of the activity is reversed.*
Counsel:	*...I think that's a common feature in inhibitors of factor Xa...that the S_1/S_4 binders can flip? And that's in the agreed common general knowledge.*
Dr Young:	*I don't believe he's suggesting they're flipping here.*
Counsel:	*I don't either. In fact...our understanding of it...was that if you look at compound 36, it does have a methoxyphenyl substituent in the top....It doesn't have a chlorophenyl group..?*
Dr Young:	*It doesn't. But I'm not quite seeing where your question is going...*
Counsel:	...[T]*he only point I'm making is that it seeps [seems?] when they talk about replacing the...the chlorophenyl group with the methoxyphenyl group...they're actually saying is that the methoxyphenyl group is replaced with the chlorophenyl group....And...if that's correct...this is also indicating chlorophenyl rather than methoxyphenyl.*
Dr Young:	*Well, Judge, I will just reiterate my position that minor changes, things can shift in the active site, the SAR in one series is not necessarily the SAR in another, that when you change your groups around - that Lego fit isn't perfect, they don't always cwtch nicely - you may just have to get a slight twist in there....*
Counsel:	*...I think your evidence has been clear about that. And I think that the agreed CGK also reflects this, that you have to test...that small changes can have significant effects on the activity of a molecule..?*
Dr Young:	*Yes.*

C. Ries and Priepke

1128. Counsel for Teva brought Dr Young next to the Reis and Priepke article (pp.1518-1519), which identifies a number of different factor Xa inhibitors, including a number of the inhibitors from the Lilly series and states, among other matters that "*In agreement with the proposed binding mode, substitution of the right 4-methoxyphenyl fragment in 54 by the 3-amidinophenyl group furnished highly active amidine 59*". Counsel suggested again that this was suggesting that swapping something else for methoxyphenyl was producing better results. To this Dr Young eventually responded as follows:

"*But you're going back to an amidine in making this change. And we've discussed for so much of the case about moving away from them. And, you know, if I was – where I was going to go with what I put there was this Lilly example, it shows you the flexibility and the diversity of things that were available to put between the two pockets, such that you could optimise your potency and your properties in your molecule, which is the most important thing for potency.*"

D. The Articles as a Whole

1129. Having run through the various just-mentioned articles with Dr Young, counsel (i) noted that (a) Dr Young, in his report, talks about the significance of the Lilly series being reported in the articles you list, (b) the foregoing are among those articles, and (ii) queried whether any of the articles considered immediately above include any efficacy data to support 4-methoxyphenyl in the S_1 pocket. There was some to-ing and fro-ing between counsel and Dr Young at this point, with counsel eventually putting it to Dr Young that "*a fair review of the papers that you've referred to in your report...doesn't lead to 4-methoxyphenyl as a good basis for further action; it suggests in a number of the papers that chlorophenyl or other substituents are in fact more potent and more active*". To this Dr Young responded as follows:

> "*I disagree with that proposition. You know, on the basis of pure potency then you may go with chloro. But if you want to get the balance of compound, or the balance of all things in your compound, you've got to be open-minded enough to think that 4-methoxy could have other things it brings to the party that the chloro doesn't. You know, having done an analysis of the application, I think you'll find that they did try the 4-chloro analogues in the P_1 position....*[I]*t wouldn't take me long to find the compounds if you so wished....but I would expect that they find that there are things that are more interesting. The skilled person would notice that....And...to pretend that these people aren't doing...the iterative process and the testing. You know, the absence of data in the patent...doesn't necessarily mean that data is absent in this*".

III. Apixaban Core as a Cyclised/Rigidified Version of the DPC-423 Core

1130. Counsel turned next to para.77C of Dr Young's witness statement, where he discusses how the core of apixaban is a cyclised or rigidified version of the core of DPC-423, states that a skilled person would recognise this modification was likely to increase affinity, and states that the "*The skilled person would recognise the similarities between the structure of apixaban and that of DPC423 (which was from the same research group).*" Counsel then led Dr Young, in summary form, through a number of (what Dr Edwards had indicated to be) significant differences between DPC-423 and apixaban, and asked Dr Young to indicate whether or not he agreed:

<u>Posited Difference #1</u>
Apixaban has a 4-methoxyphenyl in the P_1 position
Dr Young's response: *I don't disagree with that*.

<u>Posited Difference #2</u>
DPC-423 has a 3-benzylamine in the P_1 position
Dr Young's response: *Yes*.

<u>Posited Difference #3</u>
Apixaban has a lactam in the P_4 position,
whereas DPC-423 has a methanesulfonyl benzene
Dr Young's response: *Yes*.

<u>Posited Difference #4</u>
The phenyl group is aromatic, it has PP interactions
and the methylsulfonate is large and polar.

Counsel: *Would you agree with those general descriptions?*
Dr Young's response: *They are some general descriptions. But...for now we can carry on*.

<u>Posited Difference #5</u>
Apixaban has a bicyclic core, whereas DPC-423 has a monocyclic core

Dr Young: *Yes, that is an observation*.

Posited Difference #6
Apixaban has a carboxamide attached to the pyrazole ring,
whereas DPC-432 has a trifluoromethyl
Dr Young: *Yes, that is a statement of fact*.

1131. Asked whether he would call the foregoing "*significant differences*" between DPC-423 and apixaban, the following exchange occurred between Dr Young and counsel for Teva:

Dr Young: *Again, if you look at the direction of travel and the SAR in the papers on this research group...they're different. But you can see the line of sight to how they could be put together to make an active compound using all the little bits of information by bringing in from elsewhere.*

Counsel: *And I note you're talking about the research group. So, you know that this comes from DuPont and from the inventors. So, you're tracing through and understanding their work...?*

Dr Young: *It's not just their work, it's other teams as well. We are seeing other teams using the biaryl-type motif, we're seeing other groups going into P_4 and we're seeing the variations in S_1.*

Counsel: *It's commonly agreed that rigidification presents uncertainties and you can't have any real way of knowing what the effect of rigidifying a core is going to be..?*

[Though Dr Young appeared to wish to answer this last question by reference to the Pinto paper, counsel led him instead to §§108 and 115 of the agreed CGK document. Para. 108 is concerned with the strategy of trying to improve activity by rigidification. Dr Young agreed that it was a common strategy. Counsel then brought Dr Young to the last sentence of para. 108 where it is stated that "*On the other hand, if a rigid conformation does not match the shape of the active site, the strength of binding is reduced and can even be lost.*" Asked if he agreed with this sentence the following exchange ensued between Dr Young and counsel:]

Dr Young: *Yeah, but you have to look at it...in the context of WO131, which, the whole patent is about different strategies ways to rigidify this structure. And 652 is taking a preferred rigidification strategy from that publication.*

Counsel: *So, you're taking this from 131, is that it? You're saying DPC-423, from the same inventors, had certain features and then WO131, from the same inventors, rigidified, is that what you're relying on?*

Dr Young: *...I'm agreeing that rigidification as a strategy is generally a very good one. But rigidification is not guaranteed. So, if I may take you to Pinto...page 384....*[Y]*ou can see a picture there of compound 17h....*[T]*his is DPC-423. And this is their proposed binding of this compound in factor Xa. So, what we're talking about here is the strategy for rigidifying this structure to pro-organise it to be recognised by this binding site receptor within factor Xa. So, a skilled team would have a crystal structure of factor Xa. They could possibly dock this in there themselves, as I'm sure this team has done. And in 2001 you could readily just go in there, modify it* in silico*, so you would build your molecules and you would check*

the possibility of which rings may be a better strategy to do it. So, you're not doing this blindly, you are doing this rationally to try and get the confirmation that will best fit into this binding mode here. You may, I concede, allow for adjustments to get the fitting of the 4-methoxy versus the meta aminomethyl that you have in DPC-423. But we can see the direction....So it is showing you that it's not an unreasonable strategy to be rigidifying here.

Counsel: *Do any of the compounds you identified as being...compounds of note...have rigidified cores..? ....*

Dr Young: *Actually, in effect, yes.*

Counsel: *Which one?*

Dr Young: *The compound with the Diketopiperazine and the lactam structure from RPR which is the one we used at GSK....*

1132. Asked whether counsel was right in thinking that he had accepted that there are significant differences between DPC-423 and apixaban, Dr Young responded as follows:

"*There are details. But this is an aircraft...where we almost sort of staple a top deck on board it and we're just playing with the wings and things like this. It depends how you define 'significant'. They are changes. They're material changes that are probably very important to the overall outcome. But, you know, the direction of travel is there.*"

IV. Lactams

1133. Counsel turned next to §77D of Dr Young's first witness statement, which deals with lactams, is based on what goes into the S_4 pocket, and states that the S_4 binding pocket allowed for considerable variability (a point which Dr Young agreed was not in dispute and was part of the agreed CGK). At this juncture the following exchange occurred between counsel for Teva and Dr Young:

Counsel: ...[Y]*ou say that you consider it plausible that the lactam would bind in the S_4 pocket.*

Dr Young: *Yes.*

Counsel: *Is there anything about a lactam that makes that statement any way important?...*[D]*o you agree that a lactam is a common motif in medicinal chemistry?*

Dr Young: *I will answer that in a very qualified way....Dr Edwards was talking about the use of beta lactams and I pointed out he was conflating beta lactam antibiotics with lactam structures such as this. The skilled person in 2001 would've done a search of SciFinder and would've found that there are no lactams of the kind in compound 18 in any drug. I can say that with confidence because of a paper I read in 2014. So, that's not hindsight.*

Counsel: *...I'm not asking you about the antibiotics –*

Dr Young: *...I'm just saying...this paper described apixaban as being particularly novel because it had introduced two new ring structures to medicinal chemistry.*

Counsel: *This is post-priority date..?*

Dr Young: ...[Y]*es....*[b]*ut if the skilled person was looking at putting a lactam into their molecule, the skilled person could've done a novelty search, which they would've probably done in filing a patent, to show that that lactam had not been found in a drug.*

Counsel: *There's compounds in 652 that have no lactam at all in them, isn't that right? My understanding is compound 115... doesn't have a lactam....*

Dr Young: ...[T]*o my knowledge...and my checking of this patent, every single compound in here has a lactam in it or a sultam or something that you could technically quibble about but not –*

Counsel: *Sorry, just to pause you there, Dr Young. A lactam or a sultam? A sultam is not a lactam, I take it?*

Dr Young: ...[T]*hat's made very clear in my expert report that the skilled medicinal chemist would understand that sultam congener of lactam – ...the sulphonamide equivalent of a lactam – would be recognised as being a lactam. And it's explicitly set out in Embodiment 1, where they describe the scope of the patent. And that is the one thing that's constant all the way through all the embodiments.*

Counsel: ...[I]*n terms of the lactams in 652, a number of the compounds, apixaban included, have a lactam in the core, isn't that right? ....*

Dr Young: *Yes....*[I]*n Embodiments 1 to 8 where you have the bicyclic structure, I believe all of those compounds have two lactam structures.*

Counsel: ...[I]*s there anything in the patent application 652 that gives you any reason to understand why a lactam...would be expected to bind in the S_4 pocket?*

Dr Young: ...[T]*hat is not the information you disclose in a patent....*

Counsel: *....Is there any such information in this patent application?*

Dr Young: ...[T]*o answer your question, counsel, no one is suggesting that....[b]ut the skilled person would understand this....[a]nd Dr. Edwards explicitly said that a lactam is a very good isostere for a phenyl ring.*

Counsel: *And I think you have said that you can make a hypothesis that it would fit....*

Dr Young: *That's the nature of medicinal chemistry, you make the best....hypothesis you can, you keep things as small as you can and you test it. And I've no reason to believe that these people didn't do lots of testing to get what they did.*

Counsel (Teva): *You've no reason to believe they did, Dr. Young....*

Counsel (BMS): *Do you want him to answer that..?*

Counsel (Teva): *No....I'll ask the question if I need him to answer it.*

Counsel (BMS): *So, it's not a question?*

V. Frequency Analysis

1134. Counsel for Teva did not respond to this last interjection by counsel for BMS, turning instead to para 77E of Dr Young's first statement and his frequency analysis. Counsel began by noting Dr Young's observation that:

> "*The P1 and P4 groups, the carboxamide substituent and the core of apixaban are reused many times in* [the] *Application. Indeed, 32 of the compounds exemplified in the Application only have a single point (i.e. single substituent) change from apixaban.*"

1135. Counsel for Teva noted that this was Dr Young's "*frequency of use rationale*", that he says in the above-quoted text that 32 of the compounds exemplified have a single point substituent change from apixaban, and asked if Dr Young could give the same information for every other compound in the patent application? At this juncture the following exchange occurred between Dr Young and counsel for Teva:

Dr Young: *I could, but I don't have my data to hand to be able to do it. But*

the thing is, what I'm referring to there is [what] *the skilled person would see, Judge, from my frequency analysis, that by far and away the most common combinations are the two main lactams, the saturated and unsaturated versions. We can see that they're changing. A lot of things with the para-methoxyphenyl, we see those things held constant where they've changed just the P_1 group, you see the DPC-423 group, you see chlorophenyl in there, but not as many as you see para-methoxyphenyls. Then if you hold those bits together, you would see that there are lots of changes to that group that's in S_3 or R_1a, the thing I've called the jockey. And the skilled person would quickly pick that up from looking at the data.*

Counsel: ....[A]*re you starting with kind of an understanding of a compound and then checking to see how many parts of it appear how many times in the patent?*

Dr Young: ...[T]*he point I'm making...is the skilled person would recognise that we've got, if you like, the wings of our molecule; we've got the P_4 set, we've got the para-methoxyphenyl. But we're binding them into the site. And what I'm saying, and what we're talking about here, is the changes now being made to the R_3 substituent.*

Counsel: ...[Y]*ou're starting off knowing that there's 4-methoxyphenyl in the S_1 pocket and then you're looking to see the changes around it..?*

Dr Young: *The practices of the team would be very evident when you see the changes they're making.*

Counsel: *So, you're starting with knowing one of the substituents and then checking the changes around it..?*

Dr Young: ...[Y]*ou're looking at the frequency of use of the different elements....And then you would recognise the extra change is being made. And you would see that there's.....a lactam in every single one. And the only lactams that aren't the two preferred ones...are included in examples that have either trifluoromethyl and para-methoxyphenyl in that top end. So, you would quickly realise that a lot of the fine tuning is being done in that R_3 ring....*

Counsel: ...[Y]*ou prepared your witness statement for these proceedings on the basis of drawn out structures that were given to you by WilmerHale..?*

Dr Young: ...[W]*e've had this discussion before....[T]he embodiment, the two things in there were done from the structures, the other...was done from the patent. But I could easily have done this myself....*

Counsel: *....I have to put to you that there's no precedent in the literature for placing weight on a detailed frequency of use analysis like the one that you carried out....*[I]*s there any precedent in the literature that you have identified for the purpose of these proceedings for attaching weight to...frequency of use?*

Dr Young: ...[Y]*esterday we looked at the line in Lipinski describing the very strong pattern recognition skills of medicinal chemists and why Lipinski framed the rules in the way he did.*

Counsel: *That's not the question. The question is attaching significance to the outcome of a frequency of use analysis....*

Dr Young: ...[M]*y answer is, if you want to see what's happening, you can get a qualitative feel by looking through the structures. By doing the detailed frequency analysis I've done, it's the thing that I learned to do when I was working on factor Xa, is actually put a number on these things. And people will say... 'Oh, you notice that that's*

being used more than other things'...'How often is it being used?'....[T]*hat is the basis of a frequency analysis. This is what medicinal chemists would do subconsciously all of the time.....*

Counsel: *In any of the literature you've identified, does anyone attach weight to a frequency of use analysis?*

Dr Young: ...[N]*obody has said that they do that. But...you are just doing it. You don't have to write in a paper somewhere that this isn't important.*

Counsel: *And I think from what I understand, it's a kind of statistical analysis, isn't it? You're just trying to get a sense of what the inventors are most interested in, is that your position..?*

Dr Young: *...I wouldn't say there's any statistical analysis of it. It's just what's used more than others....*

Counsel: ...[T]*his is something you do just to figure out what the inventors are most interested in..?*

Dr Young: *Yes, it will give you a really good flavour of what they've used and what has worked....Because if it didn't work, they wouldn't continually use it....*

Counsel: ...[T]*he other medicinal chemists who've given evidence, including in the UK proceedings, said that they wouldn't do the type of exercise set out in your witness statement.*

Dr Young: *Well, I beg to differ then....*

Counsel: ...[I]*f you did the analysis that you identify in your witness statement...it actually wouldn't lead you to apixaban, because the CF_3 substituent is more common than carboxamide in the R_3 position..? ....*

Dr Young: *No, I disagree, because of the nature of which groups have been used in which combinations.*

Counsel: ....[Y]*ou produced your statement on the basis of the drawn out structures that you were given by WilmerHale. The night before you gave evidence, we were given, for the first time, this document that the Court will be familiar with.*[7] ....[W]*hen were you asked, or were you asked to produce this document and for what reason?*

Dr Young: *...I was first doing the analysis when I was working with Mr. Howard over a year ago when we were looking at, you know, could you generate structures from names? ....*

Counsel: ...[W]*as the purpose of this document to suggest that it was something that you could've done subconsciously, the identification of the frequency of use?*

Dr Young: ...[Y]*ou could read through it and you would notice how often the different groups were being used....*

Counsel: ...[Y]*ou knew what apixaban was when you came to work on this patent application..?*

Dr Young: *Yes.*

Counsel: ...[Y]*ou know what apixaban is and you pick up a document to try to subconsciously figure out the frequency of uses, a subconscious mind would find it very difficult not to have regard to what they know about the compound apixaban.*

Dr Young: *I...did this analysis with a totally open mind and I looked at the numbers....When you look at the frequency of use of all the groups, you quickly recognise the pattern of changes....*

[7] Although these questions were put for the sake of completeness, Teva reserved its position in relation to this document and the purpose for which it was put in. (The evidence put to Dr Edwards was not based on the document or anything BMS tried to draw from it.)

Counsel: *Pattern of changes from what?*

Dr Young: *The pattern of use of all the different groups....*[T]*wo lactams...are drawn on page 1 of this document...they're the ones that stand out. There's only four other lactams in there. You can see that they're being used. And we know that para-methoxyphenyl is the most common. You would then notice that...there are an awful lot of compounds where the single variation is in the R_3 position with both of those other two. But this is only one part of my identification of apixaban.*

Counsel: ....[I]*f you look at Figure 17 of your witness statement....*[y]*ou identify the R_3 group on the top right-hand side....*[a]*nd if you look at the...bottom left-hand corner you identify the P_4 distal ring and you identify the two lactams. You've got the most common substituent above the less common....*[a]*nd if you look at the R_3 group, you have the...the less common of the two, the carboxamide...*

Dr Young: ...[M]*y point...is that when you look at the compounds where they varied the P_1 group, many of those are done with the CF_3 in the position. And you would understand that that is different from the pattern that's prevalent in most of the compounds.*

Counsel: *Can I ask you just to turn to Figure 19 of your report..?....This is your analysis of WO131....*[a]*nd if you look at the P_1 group....you've got the most common one first and it's the second one is the less common? But your point I think you're trying to make there is that you're relying on the most common one not being the methoxyphenyl..?*

Dr Young: ...[T]*his is looking at all 110 examples....And of course, we're looking at a lot of compounds that have other variations on the structure.*

VI. Progressive Narrowing of Patent

1136. Counsel for Teva turned next to the proposition put by counsel for BMS in his examination of Dr Young that the patent narrows progressively. Turning to the patent application, counsel posited that this proposition did not hold good of Embodiments 7 and 8. At this point the following exchange occurred:

Dr Young: *But...there's a direction of travel here. It's –*

Counsel: *No...sorry, there's a specific point I wanted to put to you, which was that it had been suggested that there was a progressive narrowing in the patent application. That's not strictly correct, is it?*

Dr Young: *Well, there are 74 compounds in Embodiment 8 and, you know, as many as you like almost still in Embodiment 7. So, we are narrowing in the total scope. But we have six compounds in Embodiment 8 that are not in Embodiment 7. So, we've still got less compounds than there would be. We're playing with words really....*

Counsel: *It's just a factual correction, Dr. Young....There's extra ones...not covered by Embodiment 7....Embodiment 8....has ones that aren't covered by Embodiment 7, so it's actually not a subset.*

Judge: *But you're saying overall the number is lower, isn't that correct?*

Counsel: *Yeah, there's just 74 compounds...and I recognise that eight of them...have a variation on the lactam....I'm...agreeing with that.*

1137. At a later stage, counsel also put it to Dr Young that Dr Edwards's evidence had been to the effect that the effort involved in the synthesis of Example 18 could be explained, and that there could easily have been outsourcing done. Counsel noted too that in his oral testimony Dr Young had indicated the compound was either scaled up or outsourced, suggesting to him that this indicated Dr Young to agree with Dr Edwards in this regard. Dr Young responded that "*I don't think that's anything to dispute....Clearly, this team have done this synthesis by whichever way, multiple times, to enable them to make a lot of the compound.*"

VII. Volume of Compound Synthesised

1138. Counsel for Teva turned next to para.77F of Dr Young's first witness statement and the notion that the amount of apixaban synthesised tells the reader that apixaban was of most interest to the inventors. Counsel asked whether there was "*anything in the documents, the literature or the CGK which indicates to you that the amount of a compound synthesised indicates its plausibility or that it was the focus of the patent*". At this juncture the following exchange occurred between Dr Young and counsel:

Dr Young:	...[I]*t's what the skilled person would take from reading a patent....*
Counsel:	...[T]*he question was a net one, Dr. Young: Is there anything in any of the literature you've seen that indicates that it's common practice to attach weight to the amount of a compound synthesised?*
Dr Young:	*I don't think that's the kind of thing anyone has written ever in the literature. But it's common practice in medicinal chemistry.*
Counsel:	*Have you any basis to point to that?*
Dr Young:	*Not in writing, but....I know a lot of people who –*
Counsel:	*That's fine.*

1139. At a still later stage, counsel returned again to the weight to be attached to the amount of compound synthesised, the following exchange taking place in this regard between counsel and Dr Young:

Counsel:	*When you address, in your report, the weight you seek to attach to the amount of the compound synthesised, you don't address other possibilities. And I have to put it to you, I think in the evidence that's been given in other jurisdictions, including by yourself, there's a discussion about other possibilities. And I'm just going to put these to you and ask for your opinion as to whether they are possible reasons that a patentee may synthesise one amount or another of a compound. Could you synthesise a compound for the purpose of proof of concept?*
Dr Young:	*Yes....*[but if]*....you look through the common general knowledge, it would appear that the concept is proven for factor Xa....*
Counsel:	*Is it possible that you would synthesise more because you want to use it as a tool compound?*
Dr Young:	*Again, I will agree, with the qualification that why would you need a tool at this stage of the programme when you've got so many clearly advanced compounds in your experience already? ...*
Counsel:	[D]*o you agree that it's a possibility that you would make a compound in order to validate a particular form of test?*
Dr Young:	...[A]*s a simple statement, yes. But* [with] *the qualification I've already given you...that you wouldn't need to do it in this case.*
Counsel:	*Do you agree that you could generate more compound for the purposes of generating libraries of compounds? ...*
Dr Young:	*....I'm agreeing with you with making libraries of compounds. And*

if you would want to do it from compound 18, you would probably do it earlier in the synthesis....

Counsel: ...[W]*ould you synthesise an amount and then use it potentially for different purposes?*

Dr Young: ...[T]*hose purposes would most likely be biological evaluation to fully profile your compound.*

Counsel: *Is there any basis in this patent application to make that assertion?*

Dr Young: *There's lots of discussion about the aspirations and they talk about...what the pharmacokinetic profile is....*

Counsel: *Have you not given evidence before that that* [the pharmacokinetic profile] *was a wish list? ....*

Dr Young: *I don't know if I've used that actual term....Every time you work in a programme...you would detail all of the things you wanted in your compound. But medicinal chemistry is a game of compromises; what matters in the end is what is the dose of your drug. And you have to make compromises on many things....*

Counsel: *....I asked you is there anything in this patent application to make you think that the 3g was synthesised to be used solely for one purpose....You said that there's aspirational language in there and there's the DMPK pharmacokinetic profile. Are those matters in any way linked to Example 18 in the patent application?*

Dr Young: *There is no direct linking to say what they did with it. But I think it's just common sense to make the connections.*

Counsel: *To...draw the conclusion that the 3g was all used for one purpose, is that the conclusion you're making?*

Dr Young: *No, you're making the connection that these people are particularly interested in this compound....*[and] *profiling that compound considerably further.*

Counsel: *...Dr. Hermkens...talks about the use of the compound that's synthesised in Example 18 being used as an intermediate in examples 96 and 99 and he points out...that example 99 uses 1g of the final product, which is one-third of the amount produced in Example 18....Does that alter your views as to the significance of apixaban..?*

Dr Young: *...I'm not going to answer this in one word. I will agree that you have got a possible explanation for why it may have been done. But...when you've got to apixaban, you've done multiple steps to get there....They've got there and they think 'what can we do with this?' And...it's something of a dead end. And I think if you look at the way the chemistry has worked in these two examples, it isn't very efficient and effective chemistry. They've used a gram to make a few milligrams and they've only used a small proportion of that to get there. I will accept that they may have tried reacting multiple times to get it, but they only ever made a little bit and they probably made their decisions on that small amount of compound....And clearly, if you've got this compound and they're using this amount of it, by the time they did this chemistry – again, this might be speculation – they might've had even more of compound 18 to play with. We don't know that they've not made more. I agree that it may have come from the 3g. But you wouldn't have done recrystallisation to do the chemistry that followed, you would've used crude material, the 4g that the 3g came from. There would be no reasons within the chemistries used here to do further purifications....*

Counsel: *And I think, Dr. Young, in fairness, there's a lot of alternative*

explanations..?

Dr Young: *...I have given some. And...there are more.*

Counsel: *There are more...and if you look...at Dr. Hermkens' statement...he talks about the fact that part (e) of Example 18, which is just before the final step of the synthesis, is also used as a starting material for other compounds, so, that could indicate that they were building blocks as far as part E and then there were different outcomes they wanted to achieve and different products they wanted to make.*

Dr Young: *Well, Judge, as we saw yesterday, one of the very hard things to make is that product there that he's saying is the product of part E. That was one of the most difficult steps to make it. And you have an ester in place there and an acid. That is a position that most medicinal chemists would almost dream of; you could go away and you can make lots of analogues very easily....[Y]ou have to look at what is done in context. And the fact that they haven't made more things of this type...is probably showing you that they're not very interested in what they could make there. They may have made other things, but they haven't included them in the specification.*

VIII. The Report of Dr Hermkens

1140. Counsel put certain propositions to Dr Young that appeared in the expert report of Dr Hermkens, whom I understand is a medicinal chemist who gave evidence in parallel proceedings.

1141. Asked whether the NMR data is just a quick routine test that can be carried out easily, Dr Young indicated that "*NMR is probably some data that a medicinal chemist would gather on just about every compound you make....in quantity.*"

1142. Responding to counsel's observations that Example 18 in the patent does not give high resolution mass spectrometry data but that it is included in Examples 22 and 24, Dr Young responded that:

> "[H]*igh resolution mass spectrometry is not routinely used in drug discovery. You would often do an LC low resolution mass spec to confirm your pass....Some people may use it at some time. Sometimes you will use it....[S]ome people may use this to confirm that the reaction has proceeded as they think, because you could get other side products that maybe wouldn't be evident in NMR. It is not a routine test. Low res mass spec is usually what people use. But more often than not, NMR will be good.*"

1143. Responding to counsel's observation that there is no purity data in the patent application, Dr Young observed that although there is no data that indicates purity, there is recrystallisation data "*which demonstrates that they are looking to enhance the purity*". On the issue of recrystallisation, the following exchange occurred between counsel and DR Young:

Counsel: ...[M]*oving on to the recrystallisation, what part F of Example 18 says, as Dr. Hermkens records, is that two recrystallisation steps were carried out...and that's what Dr. Edwards has also said in evidence....*[a]*nd they both say..."On closer inspection, it seems the product from the silica gel chromatography step was split into two separate portions." So, there were two different batches. Is that your evidence also?*

Dr Young: ...[T]*hat's what appears in the write-up, yes....*

Counsel: *So, two separate batches were obtained by two separate recrystallisation steps..?*

Dr Young: *Yeah. So, what this is indicating to me, Judge, is that they're looking at one of many things, such as higher purity...to take it into further studies. They were also considering are we looking at a particular crystalline form? ....*[The] *crystalline, it's purer, so it's more active. And that's why people do crystallisations/recrystallisations in this drug discovery. Contrary to what has been said, it is not always done....in contemporary practice.*

1144. After Dr Young confirmed that there were two separate crystallisation events after the chromatography, counsel noted that Dr Hermkens had said that he would not have expected such an approach to purification and it struck him as significant that that was done. Dr Young appeared to agree.

IX. Description of Compounds

1145. Counsel for Teva asked Dr Young whether he was familiar with the idea that it is a good idea to describe well the compounds in which one is interested (a proposition that Dr Young may have posited in his testimony in Norway). At this juncture the following exchange occurred between Dr Young and counsel:

Dr Young: *Well, if you're going to publish, if you look through the publications, in that publication you sent me they've got...what you might call chapter and verse in data.*
Counsel: *Do you have any view as to why the patent holders in this case didn't include more data in Example 18 or elsewhere in the patent about apixaban?*
Dr Young: *No, the data are what they are. And, you know, I can speculate...it may be more normal to put more data. Certainly in my experience, we would add extra. But there are many examples where people would just show the NMR....And...that would be very indicative and...would confirm to you that you do have the right compound.*

X. The Nature of Dr Young's Conclusions

1146. Counsel observed that §77 of Dr Young's witness statement sets out six grounds and expressed the understanding that he accumulates them to justify his conclusion that apixaban is plausible as an effective factor Xa inhibitor. To this, Dr Young responded as follows:

"*Well, no, it's not right on its own. All of these are coming to point to you how the skilled person would come to understand that it is the most likely compound they're interested in....Some of the statements there do not address the plausibility that the compound is active and efficacious....*[T]*hese are the things that will lead you to identify compound 18.*"

15. Expert Witness's Duty of Independence

1147. Counsel led Dr Young through the conclusions in his report and those in Dr Camp's report and suggested that they bear a striking similarity. At this juncture the following exchange occurred between Dr Young and counsel:

Counsel: *Are they the same six conclusions, Dr Young?*
Dr Young: *You've asked two experts to go through and justify why this compound is what it is. And we've used the same logic.*
Dr Young: *You used the same conclusions in the same order, Dr Young. Do*

you not see anything surprising about that or can you explain it? ...

Counsel: *I have to put to you, Dr Young, that it's become apparent in the course of today's evidence that you were given material we didn't know before today you'd been given. It became evident on Monday that you had been given structures that we didn't know about before Monday and there is a striking similarity in the conclusions you've drawn in your report. I have to put to you that there's a strong obligation of independence on an expert witness and that your work should be your own, free of any interference or suggestion by others and I have to put to you that this suggests that those obligations have not been met and I have to formally put that to you, Dr Young?*

Dr Young: *...I have to disagree with that. I have used the same logic and I have drawn from the data in front of me the same inferences.*

16. W0131 and Apixaban

1148. Counsel for Teva noted that in his witness statement Dr Young expresses the view that none of the examples in 131 have a similarity to apixaban, is that right? She drew his particular attention to §91 of his witness statement where Dr Young identifies a number of factors to arrive at apixaban that he says would need to be chosen. At this juncture the following exchange occurred between counsel and Dr Young:

Counsel: *You identify there four differences that you say make it difficult to identify apixaban or make it...but I have to put to you that your evidence today has been that based on the common general knowledge 4-methoxyphenyl would be a plausible binder in the P_1 pocket....I'm not saying I accept it but that is your evidence..?*

Dr Young: *That's my evidence but I'm saying it has to be chosen from a number of different possibilities.*

Counsel: *Your evidence I think is also that based on common general knowledge...that a lactam would be plausible in the P_4 binder, I presume you say the same in relation to WO131..?*

Dr Young: *I've not said that it's a plausible P_4 binder* [...] *I've said that the lactam is a plausible isostere for a crystal ring of the P_4 core. There's a difference in that statement....*

Counsel: *Your evidence has been that a P_1 core P_4 is a plausible structure for a factor Xa binder?*

Dr Young: *Yes.*

Counsel: *And that that applies from the CGK?*

Dr Young: *Yes.*

Counsel: *And the same would apply to WO131..?*

Dr Young: *Yes.*

Counsel: ...[P]*resumably if you put those together it does answer a number of points that you make about....*[b]*eing able to get to apixaban from WO131? ....*

Dr Young: *You're saying there are many things that need to be modified between the two patents and there's that distinctly different teaching* [?]....

Counsel: *My only point is that on your own evidence three of the substituents that are present in apixaban are matters that are CGK?*

Dr Young: *But, as we've been discussing, Judge, what is really interesting about 652 is the use of the lactam in that position. It's a much smaller, lighter group put in that distal position. And...that's the*

key part and the key subject of WO652.

Counsel: *I just have to put to you that on your own evidence, Dr Young...there is no technical advance in WO652 over WO131 on the basis of your evidence?*

Dr Young: . ..[I]*f you read my report I can refute that completely because the technical distribution is in the very different profiling of the compounds of 652 compared with 131. We've talked a lot in this interview about the principle and the direction of travel and if you look, you know, I made points about...weight...size...lipophilicity. We have basic compounds in 131. We see comment in the common general knowledge from Zhu and Scarborough about the potential issues of insolubility with one of the intermediate compounds. So, they're...a body of evidence of why things are bad in 131 – or not so good....They're very likely to be very active....*[W]*hat you get from the lactam is...compounds that...*[have] *a distribution of weight and I show you the trends in lipophilicity and removing that basic centre....That is what is different between 652 and 131.*

D. Re-Examination

1149. Counsel for BMS asked three related questions in his re-examination of Dr Young. His question derived from the fact that it was put to Dr Young that he had performed his analysis with an eye on the target of apixaban, in other words, with hindsight. Counsel for BMS asked of Dr Young whether there was anything in the material in Figure 17 (or 18 or 19) other than facts drawn from the patents? At this juncture the following exchange occurred between Dr Young and counsel for Teva:

Dr Young: *No. As you see, it's just a connotation and a representation of the structure that show you the substructures I'm looking at are an account of what I have observed in that position.*

Counsel: *So, where did the information in that figure come from?*

Dr Young: *It came from my Excel sheet I kept when I made a note of the different substituents.*

Counsel: *And where did that information come from?*

Dr Young: *I looked through the structures and as I saw them, well what I did was I put nothing, or, you know, or a defining feature for that position.*

29

Some Conclusions and Criticisms

A. Some Conclusions

1150. What key conclusions might be reached as to plausibility based on the relevant evidence that is properly before me?

1151. BMS has suggested that the following conclusions fall to be drawn (though, as will be seen later below, there are, I respectfully observe, significant flaws in the position contended for by BMS):

[1] History

a. At the priority date, the only available oral therapy for thromboembolic disorders was warfarin, a drug with significant side effects and a narrow therapeutic window. So, there was a perceived need for better anti-thromboembolic treatment.

b. By 2001 almost all major pharmaceutical companies were doing research to find a better anti-thromboembolic treatment. The coagulation cascade has two logical points at which a treatment could focus, factor Xa, and thrombin.

[2] Factor Xa and Thrombin

c. Thrombin has a complex pro-/anti-coagulant role. Factor Xa is pro-coagulant. It sits at the centre of the coagulation cascade and is the sole enzyme responsible for the activation of prothrombin to thrombin. It has a high amplifying factor. Inhibiting factor Xa was expected to enable effective anti-thrombotic treatment.

d. It was known that large reductions in factor Xa activity could be induced without significant risk of hypocoagulation when clotting was required.

e. Factor Xa was identified as the preferred target for the proposed new therapy.

[3] Publications

f. By the priority date much research in the field had been published. There were important themes in this work: (i) the structure of factor Xa and its binding properties were well-known; (ii) its crystal structure had been published in 1993; (iii) it has two binding sites (pockets) located at the S1 and S4 positions; (iv) it was well established that small molecule inhibitors could be synthesised which were capable of binding to factor Xa with potency; (v) these have no relation to the natural ligands for factor Xa but prevent its action by binding with the S1 and S4 pockets.

g. Dr Edwards's literature search identified a paper by Maignan and Mikol which examined in detail the structure of numerous small molecule inhibitors which had been synthesised and reported, and a paper by Zhu and Scarborough which references two earlier reviews by the same authors. The

second, Zhu and Scarborough 2000 is an important source of information about what was commonly known about the molecules under development at the priority date.

[4] Points of Which there is No Material Dispute

h. From these reviews and other material a number of points can be established, in relation to which there is no material dispute:

(a) to achieve effective binding with factor Xa, a molecule with high potency was needed.
(b) potency measures how strongly a molecule binds to an enzyme. It is measured on two scales, IC50 and Ki.
(c) it was understood that for an effective factor Xa inhibitor, a Ki in the nanomolar range was required.
(d) it was understood that at a Ki of >10μM a candidate compound could be screened out because it bound too poorly to be worth more investigation.
(e) to be useful as an inhibitor, it was necessary to ensure 'selectivity', *i.e.* that the inhibitor did not bind with enzymes other than the target. (Teva agrees in its closing submissions that "*selectivity is a 'primary essential' characteristic of a potential factor Xa inhibitor*").
(f) to be sufficiently selective it was well-known that there should be at least three orders of magnitude difference between the affinity of the molecule for factor Xa and other enzymes.
(g) factor Xa is a serine protease. There are other serine proteases similar to factor Xa: achieving selective binding to it was initially considered a challenge.
(h) Maignan and Mikol and other publications made clear that selective binding to factor Xa could generally be achieved by suitable molecule design.
(i) all the molecules have a common structure, comprising a P1-core-P4 configuration (where the P1 substituent binds with the S1 pocket on factor Xa and the P4 substituent binds with the S4 pocket). I do not understand this to be a matter of material dispute between the witnesses, notwithstanding the observation in Teva's closing submissions that it was never put to Teva's witnesses whether there are compounds that have the P1-core-P4 structure but which are not factor Xa inhibitors.
(j) the S1 pocket was well-characterised; its shape and electronic configuration are set out in Maignan and Mikol.
(k) the S4 pocket comprises a surface cleft with hydrophobic residues as the floor and walls. It had been found to interact with a range of different binding groups on inhibitor molecules.
(l) the molecules are L-shaped with the P1 and P4 substituents angled so that they can point down into their respective pockets and bind effectively.
(m) there are areas on the surface of the factor Xa molecule adjacent to the 218 and 220 residues on factor Xa between the pockets where hydrogen bonding with intermediate parts of an inhibitor can occur.
(n) basic molecules were initially found to bind most effectively.
(o) basic molecules have poor pharmacokinetic properties; many research groups were working to find less basic and neutral molecules which would have better absorption/distribution properties and thus be more effective therapeutic agents.

(p) a wide variety of binding groups were identified which were capable of binding in the S1 and S4 pockets. Maignan and Mikol point to the fact that a neutral group, methoxyphenyl (a.k.a. methoxybenzoyl), would bind in the S1 pocket, though with less potency than the basic benzamidine equivalent.

(q) a well-known technique for improving the binding of a small molecule inhibitor was structure rigidification. This was typically done by including structures such as bicyclic rings.

(p) one key issue with small molecule inhibitors is to design them to have good biological properties, *i.e.* good solubility and permeability. (A recognised methodology for identifying at an early stage in drug design molecules likely to have such properties was Lipinski's 'Rule of 5').

(r) It was well understood that compliance with the 'Rule of 5' increased the chances that a molecule would have useful drug-like properties. So the Rule was used as a guideline for assessing molecules in initial research stages.

(s) medicinal chemists have strong pattern recognition skills. They are adept at working out from the structure of a molecule how it is likely to bond and solvate.

(t) it was appreciated that altering substituents on the backbone of the molecule could also improve potency by providing surface interactions with the enzyme.

[5] Use of Published Patent Applications

i. Published patent applications are a potentially useful source of information about the design of small molecule inhibitors, whether or not those applications contain experimental data. A number of the patent applications reviewed by Betz have no experimental data. Despite this, Betz considered them sufficiently important to note.

[6] Quest for nM potent factor Xa inhibitors

j. Dr Edwards accepted that the patents reviewed were the result of work done to find nM potent factor Xa inhibitors. It is common ground that there would be no point in working on molecules which did not have this potency and that such knowledge is something the specification reader brings to their understanding of what it teaches.

[7] Known Molecules

k. The agreed CGK document lists (at §131) five molecules which would be known to the workers in the field. There are others which anyone reviewing, *e.g.*, Maignan and Mikol or Zhu and Scarborough 2000 would have become aware of, and whose properties the person skilled in the art would have appreciated. Among them was DPC-423, previously designed and published by the research team responsible for the work disclosed in 652, widely noted, and considered a major step forward. Dr Young said (Dr Edwards agreed) that a medicinal chemist would see the lactam of 652 in the P4 position as a plausible isostere for the phenyl group in the P4 position in DPC-423.

[8] The Specification

l. A patent application/specification should be approached by a skilled reader endeavouring to understand what it discloses, *i.e.* by "*a mind willing to*

understand". The European Patent Office textbook, *Case Law of the EPO Boards of Appeal* states as follows at §6.1 at p. 337:

> "*According to the established case law, the skilled person should try, with synthetical propensity, i.e. building up rather than tearing down, to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of the patent. The patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding (see* inter alia *T 190/99, T 920/00, T 500/01, T 749/03, T 405/06, T 2480/11, T 2456/12, T 383/14, T 1477/15, T 448/16).*
>
> ...
>
> *A considerable number of decisions have held that the skilled person, when considering a claim, should rule out interpretations which are illogical or which do not make technical sense (see inter alia T 190/99, T 552/00, T 920/00, T 1023/02, T 749/03, T 859/03, T 1537/05, T 1204/06, T 681/15). Some decisions (T 1408/04, T 1582/08, T 493/09, T 5/14, T 2110/16) have emphasised that this is understood to mean only that technically illogical interpretations should be excluded. A mind willing to understand does not require that a broad term need be interpreted more narrowly (even if, as in the case underlying T 1408/04, the narrower interpretation would refer to a structure which is very common, but not exclusive, in the technical field concerned)*."

It did seem to me, with all respect, that in its written submissions Teva (i) misconstrued the notion that a patent application/specification should be approached by a skilled reader endeavouring to understand what it discloses and (ii) read into this a mistaken contention that BMS did not make (and which would not have been correct if it had), *i.e.* (per Teva) "*that the Application must be taken to contain a real invention and the only task is to find it*".

[9] The Embodiments

m. Embodiments 1 to 8 show the pattern of disclosure for embodiments with a bicyclic central core, the pattern being repeated in embodiments 9 to 15 for a single ring core. The initial embodiments are very broad. They encompass a huge number of possible molecules. However, they all have the common structure identified at the top of page 8: P4-P-M-M4. Dr Edwards accepted that this is the P1-core-P4 structure common to all the small molecule factor Xa inhibitors found by researchers.

n. Dr Edwards accepted that the M4 component of the common structure was identified as made up of three components Z-A-B, each as defined in the specification and that the B element is a lactam or a sulphur substituted lactam (a sultam).

o. Even in the broadest embodiment in the specification there is a common molecular structure and that the P4 (or M4 as in the specification) group is a lactam. Dr Young said in his written evidence that it was apparent from the disclosure that this is the lactam which is the focus in the title of the application "*lactam-containing compounds*". Dr Edwards accepted that this "*lactam is*

certainly noted in the patent". These are key features of the disclosure which the skilled reader can see from the broadest embodiment down.

p. Dr Edwards was taken through the embodiments in sequence by counsel for Teva, in the following terms:

Counsel:	*And if you were looking at a thrombin inhibitor, are there limits to the places a lactam substituent could potentially go?*
Dr Edwards:	*I'm not sure it would be hugely different. I think with thrombin as the S2 /S3 pocket which are available for binding, which are not present as such in factor Xa, so they would have somewhat similar S1 and S4 pockets. So, in principle, it could bind, the lactam substituent could bind in S1 or S4 particularly in thrombin, yes.*
Counsel:	*Thank you. Moving on then to the fifth reason relied upon by Dr. Young in subparagraph 77(e) of his witness statement. He says there: "The P1 and the P4 groups, the carboxamide substituent and the core of apixaban are reused many times in the application. Indeed, 32 of the compounds exemplified in the application only have a single point changed from apixaban. The skilled person would understand that this is because the inventors had achieved good results." So, he's saying that you would understand they'd achieved good results from knowing that and were trying to optimised properties by variations at other positions. What is your view of that evidence of Dr. Young?*
Dr Edwards:	*Well, it's fanciful, in that you could not know that the team has achieved good results, because there's no data potency selectivity ascribed to any of the compounds in the patent, nor an indication of whether it's a specific or dual inhibitor for factor Xa or thrombin. So, the frequency analysis whether, because a group is found multiple times in a patent doesn't necessarily imply that the compound is of interest. Because we don't know what compounds were left out of the patent, in terms of their frequency. And it's purely guesswork to find groups that may be of interest or compounds that may be of interest. But without data, you could not know.*
Counsel:	*And I think you say in your witness statement that he presents his conclusions from a frequency of use analysis. "While he does not explain his method for preparing this analysis, it appears that he has converted the names of compounds into structures, discarded certain of the structures which appear to differ from*

the rest, and then performed a counting exercise to identify the number of times a particular substituent is used. This would have been an enormous amount of work." And then you conclude at the end of paragraph 1.37 that: "As no data are provided for any of the individual compounds, it is no better than guesswork to conduct this review." That is your evidence, I think, Dr. Edwards, is it?

Dr Edwards: *Yes, it is. And if I may add, it is an enormous amount of work and it's prone to error, because it's a human exercise to extract this data, at least at the timeframe that we're considering. And as we've seen with the corrections, it's prone to error. And that's a natural human thing, because we all make mistakes, And I think it's important to put this into the context of what someone in a drug discovery team, as an interested person, presumably working in another company, would view with a patent such as 652 coming out. As has been said before, it was a busy area. Nearly every company, or every company in the industry were working on factor Xa inhibitors. So there would be a flurry of patents and papers and conference proceedings coming out weekly and monthly. And the team member may have an alert on their desktop, either through the company or setting up their own alert system, and they may find many patents coming through. And the value that they would ascribe to those patents, in part, is related to whether they find useful SAR in there. And useful SAR arises from the structures and data ascribed to the compounds. So, it's my view that a team member in another company, if this patent were to come across their desk the day it publishes, would lower their expectations and see less value in the patent because there's no data ascribed to the compound. That makes it a big leap of faith, a guess, as to what SAR may be real and important. So, I think the frequency analysis is something that may not have been performed by everyone, certainly on this patent, because of the relatively low value ascribed to a patent with no data.*

Counsel: *Thank you. I might ask you just to look at the actual figure that Dr Young produced on page 28 of his witness statement. This is figure 17. And we're assuming that Dr Young put an enormous amount of work into producing this data. I think that's how you described the work that would be involved in producing it, isn't that right?*

Dr Edwards: *It is a large amount of work.*

Counsel: *And I would just ask you to look at the actual breakdown and perhaps explain what you see in the figures that are ascribed to the different substituents here.*

Dr Edwards: *So, Dr Young presumably has partitioned the structure into various regions and he's looked for how many different groups in each of those regions appear. So, for example, and for no other reason than it's just in my eyeshot, the P4 proximal ring, 73 out of 74 have the phenyl ring. So, there's one compound missing from that list and it's substituted or is a different ring differently. You can see the central core, they're all listed as that structure. And I guess the intent here is to say that the higher the frequency, the more important the compound. So, the fact that there's a cyclised core would tell you, according to this analysis, that this is an important substructure within the compound. If you look at R3, for example, the highest frequency group is the CF3 , not the primary carboxamide.*

BMS notes that by embodiment 7, P4 is one of 27 possibilities and M4 (A-B) is one of two possible six ring lactams, one being saturated and the other unsaturated. The R1a substituent – the element attached to the core of the molecule – has reduced to the list of examples set out on page 61 of the specification.

[10] Embodiment 8 - I

q. Embodiment 8 is a list of 74 specifically named compounds. All have the core found in embodiment 7. Sixty-six have one of the lactams specified in embodiment 7, 43 saturated and 23 unsaturated. Forty-four have paramethoxyphenyl at the P4 (P1) which is the most common S1 binding group in embodiment 8. At the R1a position, the most common substituents are carboxamide and trifluoromethane (CF3).

r. Dr Edwards suggested that it would require considerable work to convert the 74 listed names into structures. Dr Young's evidence shows that to a medicinal chemist this task is straightforward and could be done relatively quickly.

[11] Binding Potency

s. The application contains a brief section on p.170 setting out the binding potency (10μM) at which the molecules are considered to be active factor Xa inhibitors. Dr Edwards agreed that the said passage indicates that the research team were looking for nM binding efficacy. He also agreed that the difference between 10μM and nM potency is four orders of magnitude (10,000 times) which provides acceptable selectivity. At p.172, the specification indicates that some compounds have 10μM potency against thrombin. Taken together, these teachings indicate that the authors are looking for 4 orders of magnitude selectivity between factor Xa and thrombin binding. This would be suitable to

make a molecule a candidate as an effective factor Xa inhibitor (per Dr Edwards).

[12] Lactam as Binding Group for S4 Pocket

t. The fact that all embodiments in 652 have a lactam at the P4 binding position is a clear indicator to the skilled reader that the authors have identified a lactam as a binding group for the S4 pocket. Dr Edwards agreed with Dr Young that the medicinal chemist would see the lactam in P4 as a plausible isostere for the phenyl group used by the same research group in DPC-423.

[13] Embodiment 7

u. Embodiment 7 has only two candidates for the lactam and 66 of the 74 molecules in embodiment 8 also have one of those lactams in that position. Dr Young said the skilled reader would consider that a significant indicator that these elements had been identified as suitable binding groups.

[14] Embodiment 8 - II

v. The paramethoxyphenyl binding group in the P1 position predominates in embodiment 8. It is also the largest group in the 110 synthesised examples. Dr Young says that the skilled reader would consider that a significant indicator that the group had been identified as a suitable binding group. The Roche and Lilly compounds with paramethoxyphenyl binding in S1 were also identified. The skilled reader, I conclude, would recognise in the light of the CGK that paramethoxyphenyl was a potential binding group for the S1 pocket and that the specification was indicating that it should be used.

w. The CF3 group at the R1a position was what was used in DPC-423. Dr Edwards accepted that the carboxamide group in that position was able to form hydrogen bonds with the surface of the factor Xa molecule where the 218 or 220 residues are located and would be an attractive substituent to include. He accepted both groups would be of interest.

x. Dr Edwards accepted that the pattern of work identified from an analysis of the molecules in embodiment 8 and the worked examples led to certain conclusions. He recognised the pattern of work in embodiment 8. Whilst he indicated that the conclusions were theoretical he accepted that the scheme of work they showed would be pointless if the researchers had not discovered something useful.

y. Dr Edwards agreed that the work described in the specification indicated that the workers were aiming to fine-tune the physicochemical properties of a molecule. The conclusion is theoretical because there was no data. However, theoretical conclusions based on sound scientific analysis are, in law, an acceptable means to demonstrate plausibility.

aa. Dr Edwards accepted that if the specification said that testing had been done, he would accept that it had been done, even though the results are not given. He pointed out that the testing expressly noted was at low level of potency. However, taken with his agreement that the authors were looking for nM potency and his acceptance that the pattern of work shown by the examples would be pointless unless they had discovered reasonably potent (*i.e.* nM level) binding, the conclusion that a fair-minded skilled reader would

reach was that some of the molecules in embodiment 8 and the worked examples had been found to be potent and selective inhibitors of factor Xa and that this was likely to be the case.

[15] Example 18

bb. Example 18, which is also the molecule listed at the bottom of page 69 of the specification in embodiment 8, is apixaban. It is amongst those molecules and has components which lie at the heart of the work identified in embodiment 8 and the worked examples.

[16] Apixaban as a Plausible Factor Xa Inhibitor.

cc. The final exchange in Dr Edwards' cross-examination, per counsel for BMS, is notable. He had indicated that the analysis through which he had been taken was "*inventive*". The following exchange then ensued(Day 8/28/21-29/9):

Counsel:	*Let me put it to you like this, Dr. Edwards: What Dr. Young is saying is, when you take all these indicators together, a skilled medicinal chemist approaching this document with an open mind would reach the conclusion that these workers had done some work which gave one a reasonable basis for thinking that it was likely that Example 18 might be worthwhile.*
Dr Edwards:	*If I make the assumption that it is an uninventive person that has knowledge of the area that this is addressed to, I find the five, or six indeed, steps that are combined to be outside of the remit of someone who is merely uninventive. I think it this would –*
Counsel:	*Why do you say it's inventive?*
Dr Edwards:	*Uninventive.*
Counsel:	*No, why would you say you need to be inventive to...*
Dr Edwards:	*Because these are very difficult assumptions to draw and build upon in a sequence of six things that you need to put together to come to an answer. So, I feel that isn't something that someone who is uninventive would be able to do.*
Counsel:	*What do you mean by "uninventive"? It's not creative, it's analytic, isn't it?*
Dr Edwards:	*Yes, but someone who is an uninventive scientist in the area I'm not sure would be able to come to the conclusion that each of these points is guesswork and that you combine them to come through. So, theoretically, if you were to believe each of the points and build one from the other, theoretically it's possible. But lots of things, in theory, are possible but in reality may not be the case.*

Counsel: *In theory it's possible?*
Dr Edwards: *In theory.*

dd. BMS has submitted that this exchange provides the answer to the question of whether or not apixaban is a plausible factor Xa inhibitor. Dr Edwards, BMS observes, accepts that apixaban's being a plausible factor Xa inhibitor is a theoretical conclusion that one can draw from the specification. Under the law as to plausibility, BMS observes, the test does not require prima facie proof. A reasonable scientific basis for believing that the promise may be true is sufficient. Dr Edwards, BMS posits, accepts in the above-quoted text that there is a sound theoretical basis for such a belief and that constitutes what is required to establish plausibility.

[17] Amount of Example 18 Made

ee. The fact that Example 18 was made in greater quantities than any other example in the specification, and was the only compound for which the inventors went through the additional effort to conduct a second crystallization, supports the conclusion that Example 18 is a plausible factor Xa inhibitor. This quantity was ample to carry out initial *in vivo* animal tests. Such a quantity would only have been prepared, and the extra effort made to obtain even more of it via a second crystallization, had the initial *in vitro* testing shown the compound to be of interest. Dr Young's evidence was that this was the most likely reason for such a large quantity of Example 18 to have been made and crystallised to purify it.

[18] Compliance of Example 18 with 'Rule of 5'

ff. Example 18 also complies with Lipinski's 'Rule of 5'. Hence it is more likely to have good biological properties and thus be a good candidate for oral therapy. These considerations reinforce the conclusion that Example 18 is likely to be an effective factor Xa inhibitor.

1152. All of the foregoing, BMS posits, leads inexorably to the logical conclusion that the teaching of the specification of the application makes Example 18, apixaban, a plausible factor Xa inhibitor.

B. Some Fatal Deficiencies in BMS's Reasoning

1153. Ostensibly, the sequence of logic that I have described in Part A above is persuasive. However, on closer examination of all that is before me and all the submissions that have been made, I respectfully consider that BMS's reasoning is flawed for the following reasons (which reasons have the result that BMS's contentions as to plausibility must fail):

[A] nanomolar potencies were required for a compound to have a potential anticoagulant effect (and thus potential therapeutic usefulness). Taken at its highest, the patent application asserts no more than that some compounds had a K_i of ≤ 10 μM. Additionally, there is no biological data in the application concerning apixaban. (Thus, asked whether there was any data in the patent application that tells that any specific compound has been tested, Dr Young responded "*No, there is no data point associated with any specific compound*". Thus, if I might respectfully paraphrase Arnold L.J. in his judgment for the Court of Appeal in *Sandoz Ltd* v. *BMS Holdings Ireland Unlimited Company* [2023] EWCA Civ. 472 (at §105) while apixaban may have been one of the compounds tested, it also may not. The application does

not disclose expressly or impliedly that apixaban has been tested and found to have Ki of <10 μM (let alone nanomolar Ki). In the absence of any theory based on *e.g.* its structure or any data in the specification, there is simply nothing in the application to support the assertion that apixaban is a factor Xa inhibitor, let alone a factor Xa inhibitor of sufficient potency to be useful in therapy.

This point [A] alone, it seems to me, suffices to render the application invalid for lacking plausibility.

[B] In his written evidence Dr Gallagher opines that selectivity over other serine proteases is an essential quality of a factor Xa inhibitor; and he was not cross-examined on this point. Thus, Dr Gallagher opines in his first witness statement:

> "*Compounds which are potentially useful as FXa inhibitors also need to be selective for FXa over other enzymes in the body. As noted previously, FXa is a member of a large family of enzymes called serine proteases. Serine proteases are not only present in multiple parts of the coagulation cascade but they are ubiquitous throughout the body and regulate diverse functions. So it is crucial to make sure the compounds are very specific for FXa and do not inhiblt other serine proteases to any significant degree. This is because….(b)* [t]*o have anticoagulant activity, an FXa inhibitor must be selective over other enzymes in the coagulation cascade to avoid the risk of inhibiting naturally anticoagulant enzymes (such as Protein C and Protein S) because to do so would directly counteract the desired property which is to act as an anticoagulant. Likewise, off-target inhibition of enzymes that are part of the fibrinolytic system (such as plasmin, urokinase and plasmakallikrein) would likely create problems in that clots would persist.*"

Dr Gallagher's evidence chimes in this regard with the evidence of Prof. Morrissey when he was cross-examined in London, where the following exchange occurred:

> *Q.* *Trypsin is also, of course, a trypsin-like serine protease. That is an enzyme that breaks down protein in the gut. It is a digestive enzyme, is it not?*
> *A.* *That is its major role, yes.*
> *Q.* *It sounds like there were other roles as well? Did you want to –*
> *A.* *There are multiple trypsin genes, and there are reports of some of them being expressed in other tissues. There were also trypsin in those tissues that are much less clear. The best known role of trypsin is digestion of food in the small intestine.*
> *Q.* *Because of the relationship between serine proteases, trypsin-like serine proteases, it was known that many factor Xa inhibitors, to a greater or lesser extent, inhibited other serine proteases, trypsin-like serine proteases, did they not?*
> *A.* *Yes.*

Q. And that needed to be tested for?

A. Yes.

Q. There are good reasons why factor Xa inhibitor should not interfere with the activity of trypsin, focusing on trypsin initially, because, of course, if it is given orally it is going to be coming in contact with trypsin in the gut; yes?

A. Yes, if we are talking about the use of these anticoagulants in terms of administration to patients, then selectivity against trypsin is important. If you are talking about using them as an anticoagulant in test tubes in which you draw blood, then inhibition of trypsin would be irrelevant. I agree with the goal of treating thromboembolic diseases selectivity against other serine proteases it is important.

Q. Indeed, we could go further than that and say it is crucial?

A. It is very important, I agree.

It also chimes with Prof. Morrissey's observations as to published data in Zhu and Scarborough concerning the potency of candidate compounds against two fibrinolytic enzymes known as tPA and plasmin:

"*Q. If you want to reduce clotting, or a thromboembolic disorder, the last thing you want to do is inhibit the natural fibrinolytic process. You want to avoid doing that like the plague, do you not?*

A. Avoid it like the plague, I am not sure, but it is not a good target to go after I agree. So you want selectivity of those proteases in the fibrinolytic system.

Q. If you go back to page 82, so back in Zhu & Scarborough....[i]n the bottom left-hand column, page 82, we were just looking at the rabbit data, if you recall. If you drop down, then there is then a reference to DX-9065a from Boehringer Mannheim. If we drop down to the next paragraph, there is a reference to Yamanouchi using DX-9065a. Then we can drop down to the very last word of that column, and it says....[t]hey are talking about the Yamanouchi program.'This program has produced YM-60828', and there is an alternative salt, 'as a development candidate. This compound is structurally very similar to DX-9065a but is much more potent against free FXa ... and FXa in the prothrombinase complex', and the figures are given, 'and is significantly easier to synthesise. YM-60828 does not significantly inhibit thrombin ... t-PA ... or plasmin." *The importance of tPA and plasmin, they are not just picked for academic interest, the importance is that they are fibrinolytic enzymes, are they not, and you do not want to inhibit them if you are trying to produce an anticoagulant; that is correct? That is why there is references to them; yes?*

A. *That is largely correct. You want the net effect of your anticoagulant to be indeed anticoagulant, and it is strongly inhibited in the fibrinolytic system it would not have a net anticoagulant effect.*"

Still later, the following exchange occurred between counsel for Teva and Prof. Morrissey:

"*Q.* *Let us have a look at another one....This is a paper by Rai, 2001, a medicinal chemistry paper....So 104, left-hand column: 'Trypsin-like....enzymes are involved in numerous physiological processes in the body. Specifically many of....the enzymes involved in thrombosis and fibrinolysis are trypsin-like. For a putative drug to have a favourable pharmacological profile, selectivity against anti-targets is critical. Several reasons for endeavouring to achieve thrombin selectivity has been outlined earlier. Plasmin mediates fibrinolysis, the process of blood clot to dissolution, and therefore a potential anticoagulants should be selective against plasmin. Selectivity against trypsin is important for favourable pharmacokinetics due to the high concentration of trypsin in the gut.' Again, we have another author here emphasising that it is important to show that you are selective against the potential anticoagulant components, including plasmin, and those involved in fibrinolysis. So this was very much in the thinking of the skilled person, again in 2001, was it not?*

A. *Yes, I agree.*

Q *...If you are interested in a putative candidate for treating thromboembolic disorders, an acquired characteristic of that candidate must be that it is selective over fibrinolytic enzymes, and selective over trypsin.*

A. *Yes, those are important properties.*

Q. *They are not only important, they are necessary properties, are they not?*

A. *Yes. The degree to which they are selective can be debated, but it is important. It is very important that they are selective, I agree.*"

So, in London (and for the reasons stated previously above I did not hear from Prof. Morrissey in Dublin and counsel agreed that I could have regard to his written evidence in these proceedings and his oral testimony in London) Prof. Morrissey repeatedly agreed that selectivity over other serine proteases is a key characteristic of any potential factor Xa inhibitor. (And the reason for this, as Prof. Morrissey agreed, is relatively obvious, even to the lay reader. For if a compound also binds to other serine proteases, it may have a net *pro*coagulant effect).

Additionally, I note that Dr Young indicated that it is necessary to test for selectivity, as can be seen in the below-quoted exchange with counsel for Teva:

Counsel: *You've just mentioned the question of selectivity and I think it's common case, isn't it, that if you're dealing with a factor Xa inhibitor you do need to be careful to ensure that you're not also inhibiting other serine proteases; you need to test for selectivity, don't you?*

...

[Dr Young gave what might respectfully be described as a somewhat circuitous response to this question, so counsel returned again to the point with the following question]

But the overarching point is that you'd need to test and know about it, wouldn't you? You need to know if there's a risk that your factor Xa inhibitor is having an –

Dr Young: *As I said just now, you may do it late on, you may do it early you at least want to benchmark your series,*

and Dr Edwards, when under cross-examination accepted a similar point. Asked if potency and selectivity were "*only the primary essential characteristics of an effective inhibitor*" he answered simply "*They are*". So in truth it appears to be common ground in the case before me that selectivity is a primary essential characteristic of a potential factor Xa inhibitor. Yet no data is presented in the application regarding selectivity and no real reason offered to think that apixaban is a suitable therapeutic.

Point [B] alone, it seems to me, suffices to render the application invalid for lacking plausibility.

[C] I indicated that I would return to point [17] of Teva's reasoning as described by me above. It is important to note exactly what Dr Edwards says at this point. Thus, the exchange between him and counsel for BMS goes as follows:

Dr Edwards: ...[T]*heoretically, if you were to believe each of the points and build one from the other, theoretically it's possible. But lots of things, in theory, are possible but in reality may not be the case.*

Counsel: *In theory it's possible?*

Dr Edwards: *In theory.*

The points that Dr Edwards is referring to in this regard are the points made by Dr Young in his written evidence (at §77; the issues he touches upon are considered throughout this judgment) as to why, in his opinion, it would have been plausible to the skilled person that apixaban was "*an effective (and improved...) factor Xa inhibitor*". But Dr Edwards, in his written evidence, makes the point (which I do not understand him to have resiled from in his oral testimony and which I in any event respectfully accept as correct) that "[T]*his conclusion would not be reached by the skilled*

medicinal chemist because there are no data to support the contention that compound 18 was apixaban, nor is there any biological data to suggest this compound is effective as a factor Xa inhibitor." It seems to me to be clear from the stance adopted by Dr Edwards in this regard that in his answer to counsel he is stating no more than the obvious truth that one can theorise as to anything – absolutely anything – and that he was not resiling from his express written disagreement with Dr Young, *i.e.* Dr Young's answer highlights the *un*reality of what counsel was positing.

[D] As to point [18] in Teva's reasoning, I respectfully do not accept that the patentee identified 3g of Example 18 so that, at some future time (in fact over two decades later) it could be contended that that renders plausible (or even supports a finding of plausibility) of the utility of Example 18 as a therapeutic. In this regard, I cannot but respectfully agree with Teva's closing written submission that these are "*points of happenstance*" which give every appearance of having been "*seized upon...some two decades after the document was filed. They are not a technical disclosure.*"

There are in any event a number of difficulties that seem to me present in terms of attaching significance to the synthesised amount of Example 18, even for (as I now understand BMS's submissions to be) the supporting role that it plays in supporting a finding of plausibility which it contends can otherwise found to present. The biggest issue that presents is whether it is significant at all. In his examination-in-chief, Dr Gallagher indicated in the following terms that he had not noticed the synthesised amount when he read the application:

> Counsel: *In paragraph 4.2* [of Prof. Gallagher's second witness statement], *what is said there, you note paragraph 88 of Prof.* Morrissey's, *where he said it had been shown to him that 3.07 grams of compound in example 18 was synthesised. You say this was not something that you noticed from reading WO652, nor do you think this information would've been important to an skilled pharmacologist. "*The reason is that the synthesized quantity does not tell the skilled pharmacologist anything about the pharmacological properties of example 18. The skilled pharmacologist is unable to make any sort of prediction as to the potency, selectivity or other characteristic of example 18 without merely speculating.*" Does that summarise your evidence in response to Prof. Morrissey's evidence?*
>
> Dr Gallagher: *Yes*, that's *correct.* There's *no data there.*

Dr Young, when under cross-examination, essentially accepted (i) in the following exchange that the 3g of apixaban could have been used for various purposes:

> Counsel: *Could you synthesise a compound for the purpose of proof of concept?*
>
> Dr Young: *Yes*.
>
> ...

Counsel: *Is it possible that you would synthesise more because you want to use it as a tool compound?*
Dr Young. *Again, I will agree...*

...

Counsel: *So, do you agree that it's a possibility that you would make a compound in order to validate a particular form of test?*
Dr Young: *Judge, as a simple statement, yes...*
Counsel: *Do you agree that you could generate more compound for the purposes of generating libraries of compounds? ....*[I]*n your first witness statement, in fact....*[y]*ou said it was "common for chemistry teams to employ techniques of multiple parallel synthesis to generate arrays or libraries of compounds." So, is that one reason, that you could make more of one compound than another?*
Dr Young: *Yeah....I'm agreeing with you with making libraries of compounds,*

and

(ii) in the following anecdotal evidence that different chemists take different approaches when it comes to synthesised quantities:

> "[F]*rom past experience, there was a class of cultures when GSK was made from Glaxo Wellcome and Smithkline Beecham and to an extent the things were mixed up and the factor Xa programme was reporting in to quite an old fashioned guy from SB and he used to jump up and down at this and, you know, blow steam out of his ears, because we were always telling him 'Well, we will go back to make a bit more of this one to get DMPK'. Because the way we were working was almost like the fail fast; get as much information as you can on as little amount of compound as you can to make more analogues to understand your SAR, your SPR, before you would commit to going to do that experiment. You could get your anticoagulant activity on very little compounds. And that was very big market for us. It's what you term potency. It's the first line into efficacy. It's understanding how much of your compound is getting -- or it needs*",

and

(iii) in the following exchange that NMR spectroscopy is carried out on almost every compound a medicinal chemist makes (unlike high-resolution mass spectrometry, which is not routinely used), the significance of this point in the present proceedings being that Example 18 is characterised by NMR alone:

Counsel: *I'm going to ask you to look at the expert declaration of Dr. P. Hermkens that was submitted in related proceedings in the Netherlands.... And there's a number of points in this document that relate to the patent application that I need to just address with you.... The first one is that the NMR data is just a quick routine test that can be carried out easily. Do you disagree with that?*

Dr Young: *NMR is probably some data that a medicinal chemist would gather on just about every compound you make -- 483 Q. Exactly. A. - in quantity.*

Counsel: *In Example 18, it doesn't give high resolution mass spectrometry data, does it?*

Dr Young: *So, high resolution mass spectrometry is not routinely used in drug discovery. You would often do an LC low resolution mass spec to confirm your pass.*

Professor Taft, I note also attaches weight to the synthesised amount; however, his evidence suffers from the unfortunate deficiencies that I have outlined previously above (here that his knowledge of the synthesised amount rests on his having been told of this by Dr Camp who has not been a witness in the present proceedings).

Although I understand that Meade J. was confronted with the argument that the 3g synthesis offered a sufficient basis in and of itself to ground a finding of plausibility (whereas I understand the closing submissions of BMS to relegate it to a supporting role in this regard) I nonetheless take some comfort in the fact that Meade J. was at least as sceptical as me as to the overall significance of the 3g synthesis, observing as follows, at §§164-172 of his judgment under the heading "*3g quantity of apixaban*":

"*164. As I have already said, apixaban is Example 18 in 652 and at page 222 line 25 it is identified that 3.07g was ultimately made. Although the Claimants raised some minor questions about the reporting of the quantities reported in the stages of the work I did not think they undermined the conclusion that of the order of 3g was made.*

165. In addition, I find that that was the most of any compound reported to have been made in `652, by some distance.

166. There is no explicit disclosure of why the patentee made that amount. BMS said that the reader would infer that it was because early results had been favourable and the patentee wanted to take work on the compound forwards. The evidence of the DMPK experts (this was an isolated instance where their evidence was relevant) was that this was possible, with the further work intended being, possibly, second species pharmacokinetics or early toxicology.

167. The Claimants responded that there were other possible reasons, such as making apixaban as an intermediate on the way to making something else

(although Dr Redshaw could not make any concrete suggestion) or as a thrombin inhibitor, which seems possible given the teaching of `652 on that topic, if not especially likely.

168. In cross-examination Dr Camp was taken to a 2003 publication by Scott Sheehan of Lilly ("A four component coupling strategy for the synthesis of D-phenylglycinamide-derived non-covalent factor Xa inhibitors") where a similar large amount was made of a compound which was not successful. He accepted on the basis of it that the amount of a compound made could not be taken as an indicator of success in every case; one possibility was just that "the chemistry worked better".

169. There was, Dr Camp accepted, no evidence in any of the CGK review articles of the authors selecting compounds for review or inclusion based on the amount made.

170. In her oral evidence, Dr Redshaw maintained her overall position that judgments could not be made about a compound's qualities from the amounts made.

171. The 3g point is not completely without relevance. It is a point which, unlike other aspects of BMS's case, is relatively free of hindsight, in the sense that it sets apixaban apart from the other exemplified compounds based on information in `652 itself that I think the skilled reader would notice.

172. However, in its substance it is a very weak point. Lacking any data, one does not know why the patentee made such a quantity and reasons other than factor Xa inhibitory activity are real possibilities. And I do not see how the point can go any further than that the patentee thought that apixaban was promising. A bare assertion to that effect in `652 (bare in the sense of lacking data or reasoning) would not have been any use in establishing plausibility, as is clear from the second point in [37] in Warner-Lambert. But `652 does not even contain such an assertion",

with Arnold L.J. striking a similarly sceptical tone when the matter went on appeal to the Court of Appeal (which affirmed the judgment of Meade J.), Arnold L.J. observing as follows at §§101-103 of his judgment in *Sandoz Ltd* v. *BMS Ireland Unlimited Co*:

"*101. There is no dispute as to what Example 18 says, however, or what the highlighted statements mean. The issue is what the skilled team would think the patentee's reason was for making 3 g of apixaban given that no explanation is given in the Application. Counsel for BMS argued that the skilled team would infer that this was because early results had been favourable and the patentee wanted to take work on the compound forwards. The problem with this*

argument is that the judge made a finding, based on the expert evidence, that the skilled team reading Example 18 would think that, although that was a possible explanation, there were other possible reasons why the patentee had made such a large quantity of apixaban. Counsel for BMS did not submit that the judge's finding as to the existence of other possible reasons which would occur to the skilled reader based on their common general knowledge and their reading of the Application was not open to him on the evidence. It follows that the skilled team would not draw the inference for which BMS contend. I would add that BMS's argument presupposes that the patentee had carried out a prior synthesis of apixaban to that reported in Example 18, whereas there is no hint of that in the Application.

102. Counsel for BMS also argued that the judge had not taken into account the second recrystallisation performed in Example 18. It is true that the judge did not mention this, but it does not assist BMS. It is clear from Example 18 that the extra step of recrystallisation was performed in order to increase the yield. Thus this adds nothing of substance to the disclosure that a much greater quantity of apixaban was made than of any other compound. [The last two sentences apply with equal rigour in the proceedings before me].

103. It follows that the judge made no error in his assessment of the significance of Example 18. Indeed, I agree with it".

[E] I have treated previously above with the 'direction of travel' argument to the extent that it is being made, if it is being made, and I am not sure from Teva's written or oral closing submissions that it is being made. This line of argument was, I understand, abandoned in the United Kingdom as not legitimate. So for it to be raised now by BMS, in Ireland (if it is being raised and whatever about BMS's opening submissions, there is no suggestion in its closing submissions that it is), that would yield that "*disquieting*" shift of position in different jurisdictions to which Collins J. refers in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ltd* v. *Boehringer Ingelheim Pharma GmbH & Co. KG* (at §184) when dealing in that case with the stance adopted by Boehringer in Ireland and the Netherlands.

[F] Dr Young was an engaging and impressive witness and is a scientist of considerable distinction. Respectfully, however, I am not persuaded as to the value of his (well-intentioned) 'frequency of use' analysis to these proceedings. A number of deficiencies seem to me to present as regards using the analysis to suggest or support a finding of plausibility.

First, he was unable to point to a paper in which significance was attached to this form of analysis. Asked whether, in any of the literature that he had identified anyone attaches weight to a frequency of use analysis, Dr Young indicated that "[N]*obody has said that they do that*", though he maintained that this *is* something that a medicinal chemist does ""[Y]*ou are just doing it.*" There is, it is true, a single remark in Betz that a particular

substituent is used frequently but I do not see in that an endorsement of Dr Young's style of frequency of use analysis.

Second, at best Dr Young's frequency of use analysis shows that a person or persons found compounds to be of interest in a general sense: it does not show that they found them of use as factor Xa inhibitors or potential therapeutics.

Third, Dr Edwards, another impressive expert witness was actually quite damning of Dr Young's frequency of use analysis, dismissing it as "*no better than guesswork*" (and possibly – I make this point myself – tinged with a degree of hindsight knowledge as to the invention). In his second witness statement, Dr Edwards states as follows:

> "*…Dr Young states that 'Based on the repeated use of this core and an analysis of the frequency of the substituents used (such as that shown above), a skilled medicinal chemist would recognise the preferred substituents and where changes were focussed to secure potency and/or optimal pharmacological and physicochemical properties'. However, this analysis does not teach the skilled medicinal chemist anything about the potency or other properties of the compounds. As no data are provided for any of the individual compounds, it is no better than guesswork to conduct this review.*",

and in the course of his oral testimony, he effectively repeated this point during the following exchange occurred with counsel for BMS:

> Counsel: *What Dr Young says at the end of paragraph 66 is that: "A skilled medicinal chemist would recognise the preferred substituents and where changes were focussed to secure potency and/or optimal pharmacological and physicochemical properties." You would agree with that as an analysis of what the pattern of work shown in that diagram illustrates, wouldn't you?*
>
> Dr Edwards: *In and of itself, it would. You would ideally like to see that in combination with activity data to put this in context, because this is guesswork at the end of the day*.

Fourth, Dr Edwards, I note as I read the transcript, touches in the next sentence of this exchange on a point that I was about to touch upon, namely that "[I]*n fact, relying on those frequencies with the R_3 group actually point way from compound 18, because the most frequent substituent is the F_3* [*sic* – I believe this should be CF_3 (not, I note, the carboxamide of Example 18)]".

Fifth, following on from the last point, the parties will recall that I questioned in the following terms at what point in the recitation of compounds one gets into the realm of patentability:

> Counsel: *As we saw in the evidence yesterday and the day before from Dr Edwards, the specification starts with a broad description covering billions of compounds. However, they all share two characteristics; they have the L-shaped P1 -core- P4 structure and they all have a lactam*

or a sulphur substituted lactam in the P4 position. Neither of these propositions is contentious. There's no dispute about them at all....

Judge: *How reduced is 'reduced' before you get into the realm of patentability?*

Counsel: *I'm sorry, Judge?*

Judge: *How far must we reduce from the billions down to some lower number to enter the realm of patentability?*

Counsel: *Well, as I said at the outset, what we are concerned with is one compound. What I am submitting to you is that the skilled reader approaching the document will see the focus of the teaching drive down to a small range of compounds - those in Embodiment 8, which is 74 compounds. And at that level one could, in my respectful submission, take the view that all of those may be rendered plausible.*

I cannot but respectfully observe that this seemed and seems a weak enough proposition. The mere recitation of compounds would not suffice to confer plausibility on all of them and if the point being made is that grouping them somehow assists in rendering them plausible, I respectfully do not see how this is so where plausibility has not been established for any of them.

Sixth, as Teva notes in its written closing submissions, Dr Young's frequency of use analysis, with respect, "*does not provide a scientific reason. It proceeds from an assumption about the commercial backdrop to the application. It does not describe a specific action on a metabolic mechanism of the sort described by Lord Sumption* [in *Warner-Lambert*]".

Seventh, I take some comfort in the fact that Dr Camp, who seems to have been presented with a similar form of frequency of use analysis in the United Kingdom met with a similarly sceptical response from Mr Justice Meade. Thus Meade J. describes the evidence with which he was greeted in the following terms, at §§181-183 of his judgment:

> "*181. Dr Camp called the lactam on the left side of the two options above "Lactam 1" and that on the right "Lactam 7" in an analysis which he then did and which was set out in his exhibit NPC26. NPC26 covers 131 compounds, of which 74 were synthesised (those in Embodiment 8). Rather confusingly, Dr Camp referred to M_4 as R_3, to P_4 as R_2 and to R^{1a} as R_1 in his exhibit NPC26.*
>
> *182. Once organised in this way it is possible to analyse, Dr Camp said, the pattern of what the patentee did. BMS submitted that of the 74:*
>
> *182.1 lactam 1 was by far the most common lactam in the M_4 position (42 instances, the*

next most common, lactam 7, having been used 24 times);

182.2 *4-methoxyphenyl was by far the most common substituent in the P_4 position (44 instances, the next most common, 3-chlorophenyl, having been used 6 times); and*

182.3 *CF_3 was the most common substituent in the R^{1a} position (20 instances, the next most common, carboxamide, having been used 13 times).*

183. *And it further submitted that the skilled* medicinal chemist would realise that *apixaban:*

183.1 *has the most common lactam in the M_4 position, i.e. lactam 1;*

183.2 *has the most common substituent in the P_4 position, i.e. 4-methoxyphenyl; and*

183.3 *has the second most common substituent in the R^{1a} position, i.e. carboxamide.*

184. *This was very elaborate work, and one of its steps involved drawing the compounds starting from their names, so as to be able to identify what core and functional groups they had*"

and then moves on to observe as follows, at §§187-192 of his judgment:

"*188.* *However, the utility of the analysis is quite another matter. I do not think there was any evidence that it was CGK to use this kind of frequency analysis to work out which compounds from a broad range were active, or promising. A crucial point to appreciate is that the analysis was done without any biological data to ground it. Dr Redshaw said, and I accept, that she had never analysed a set of compounds like this for which there were no biological data, and that there were many reasons why particular substituents might be frequently used, not just activity.*

189. *Dr Camp accepted in essence that lacking biological data the skilled medicinal chemist would not have done this sort of exercise and that the exercise was "just really understanding the issues that they [the authors of `652] are trying to resolve". So he retreated a long way from his written evidence.*

190. *Even taking this analysis along with the indication from page 170 of `652 that some positive results existed does not help BMS. One simply cannot infer which if any*

of the 74 compounds had good biological results, which had bad results, and which had no results. Nor can one infer whether the "typical" compounds all behaved the same, or similarly. As Counsel for the Claimants put to Dr Camp at one point, this is SAR (structure-activity-relationship) analysis without any "A".

191. The Sheehan paper to which I have referred above in relation to the 3g point was again put to Dr Camp on this part of the case. He accepted that it showed 25 compounds with a particular structural feature having been made, with consistently unpromising results. This supported the Claimants' position for similar reasons. Again, and as with the 3g point, Dr Camp did not identify any of the review papers from the factor Xa inhibitor art deploying frequency of use to identify promising compounds.

192. I also thought that Dr Camp's oral evidence illustrated that this part of BMS's case was artificial in working backwards from apixaban specifically, and the later knowledge that it is indeed a potent factor Xa inhibitor".

C. Some Additional Points

i. *RIM* and *HP*

1154. In its opening submissions, at §6.11, Teva submits as follows:

> "*We contrast disclosure with the process of detective work in which BMS seeks to engage to supplement the thin technical teaching in the Application. However, it is not the role of the skilled person to approach the disclosure of a document by applying 'hermenutical stress' or 'imaginative reconstruction' to ascertain what the author must have been trying to describe – see* RIM UK Ltd *v.* Motorola Inc. *[2010] EWHC 118 at §124*".

1155. When one goes to *RIM* almost the entirety of §124, (including the words that Teva has deployed in its submission) comprises a quote from the judgment of Pumfrey J., as he then was, in *Hewlett Packard GmbH* v. *Waters* [2002] IP&T 5 (Ch.). So I will briefly consider *Hewlett Packard* and then return to the decision in *RIM*.

1156. In *Hewlett Packard*, the first claimant was the proprietor of, and the second claimant an exclusive licensee under European Patent, EP (UK) 0309596, entitled '*Pumping apparatus for delivering liquid at high pressure*'. The patent was concerned with a pump suitable for use in a particular analytical technique used in chemistry, called high-performance liquid chromatography (HPLC). The defendants petitioned to revoke the patent, on the grounds of anticipation and obviousness. The principal item of prior art relied upon was US specification 4,681,513 (Saito), which described a two-stage pump for use in HPLC. The claimants alleged (unsuccessfully) that the defendants' pump (the Waters pump) infringed the patent. It was when dealing with the question of anticipation that Pumfrey J. observed as follows, at §32:

"*Mr Wyand submitted that it is the task of the court to determine what Saito clearly and distinctly taught the skilled person at the priority date, not what can be read out of Saito by the application of hermeneutical stress. This admirable phrase concisely describes the process of squeezing a document to extract every last drop of meaning. The submission is correct: to anticipate, a document must contain a clear description of, or clear and unmistakable directions to do or make, something within the claim: see* General Tire & Rubber Co *v.* Firestone Tyre and Rubber Co Ltd *[1972] RPC 457. When considering obviousness, on the other hand, ambiguities in the disclosure of the document may be obviously capable of resolution in a particular way without the exercise of ingenuity: but it is not legitimate to try to resolve obscurity by an exercise in imaginative reconstruction to ascertain what it was that the patentee must have been trying to describe.*"

1157. In essence, what Pumfrey J. eloquently identifies in memorable terms is the uncontroversial proposition that it is not appropriate to try and read into a document things that are not in fact there. (Pumfrey J. later went on to conclude, amongst other matters, that he did not consider the impugned claim to be anticipated by Saito).

1158. In *RIM*, the claimant (RIM) was part of a group of companies behind the well-known 'Blackberry' wireless handheld devices and the infrastructure and software required to operate them. The defendant (Motorola) alleged that two systems operated by RIM allegedly infringed one of its patents, namely European Patent (UK) No 0818009 entitled 'Beletic'. In his judgment, Arnold J., as he then was, held that there was no infringement of Beletic and that Belectic was invalid for lack of inventive step over the prior art. In the course of his judgment (at §124) he referred with approval to the above-quoted observations of Pumfrey J., and if one looks at the facts of *RIM*, 'document-squeezing' is exactly what was at play in that case: it was being argued that a concept nowhere mentioned expressly in the document ('command translation') could be extracted from it by cross-referencing the claims (which did not mention the term but were wide enough to cover its use) with the description. Arnold J. rejected this attempted imaginative reinterpretation, observing as follows, at §§125-126:

"*125. In order to ascertain what invention Beletic discloses, a good starting point is the section of the specification headed "Summary of the invention", since the skilled reader is entitled to assume that it summarises the invention. Other than by means of the cross-reference to the claims, this does not mention command translation at all, let alone application level command protocol translation. On the contrary, what is presented as being the invention is essentially the architecture of the system. Even when the reader comes to paragraph [0015], which discloses "an important technical advantage of the present invention", there is no mention of command translation at all, let alone application level command protocol translation.*

126. When pressed as to where Beletic disclosed application level command protocol translation, counsel for Motorola relied most strongly on the claim. He reminded me that it was the function of the claim to "define the matter for which protection is sought" in the words of Article 84 of the European Patent Convention , which of course I entirely accept. As noted above, it is common ground that the words of the claim are broad enough to cover application level command protocol translation. It does not follow that the claim discloses it: see A.C. Edwards Ltd *v* Acme Signs & Displays Ltd *[1992] RPC 131 . In my judgment the claim does not disclose it. The claim is entirely unspecific as to the level at which the command protocol translation occurs."*

1159. In the present case, neither party has suggested that I should read into any document things that are not in fact there. I am simply being asked whether (i) what is found in the specification

read in the light of the common general knowledge (ii) provides the skilled reader with information which gives him or her a reasonable expectation that the promise expressly held out by the specification (that some of the compounds disclosed are effective factor Xa inhibitors) will turn out to be true. In evaluating the content of the specification to determine whether the one particular compound ultimately claimed can be identified from the application as reasonably likely to be an effective factor Xa inhibitor, it is legitimate and necessary to read it with a willingness to ascertain what it is the applicant for the patent has done and why. Proceeding so does not require that, and has not involved me in, 'document-squeezing' of the type that is contemplated (and frowned upon) by Pumfrey J. in *Hewlett Packard* and Arnold J. in *RIM*. The foregoing also suffices to deal with Teva's submission in its opening submissions in which it contrasts disclosure with "*detective work*", a concept which it does not define but the sense of which I believe I understand, albeit that, with respect, I am not persuaded that the use of undefined colloquialisms assists in the analysis of complex matters such as that now presenting.

ii. Modelling

1160. I am not sure how much (if any) reliance is being placed by BMS on molecule modelling as a process with predictive capacity (as touched upon in the cross-examination of Dr Edwards). Two points arise to be made in this regard. First, there is no modelling in the application, so there is no relevant teaching (in support of plausibility or otherwise). Second, in the below-quoted exchange with counsel for Teva, while under re-examination, Dr Edwards, while acknowledging that modelling can work, essentially rejects the notion that modelling has predictive capacity because it is guesswork:

> Counsel: ...[C]*an you explain to the court what is modelling?*
>
> Dr Edwards: *Molecular modelling? So, this is a computer-based technique to try and capture the structure of an enzyme, a protein, binding pockets and ideally recapitulate what you would see if you had an X-ray structure, which is more of the gold standard, it is what you would ideally like. We know at this time, although I think they potentially existed, getting routine X-ray structures of compounds bound to factor Xa was difficult or impossible. I believe that came later. So, you might use something called a homology model; you might take a related serine protease, like trypsin, for example, for which you do have an X-ray and you would chain the relevant amino acids in the protein chain and model that to a lower energy confirmation and it would twist the protein, and then you would get a slightly different shape in binding pockets, potentially. And that is what you would use to dock compounds in. So, you take your inhibitor, get a lowest energy confirmation, or a low energy confirming and, using a computer, add that compound into the binding pockets. It can work, but it's difficult sometimes, because it's guesswork...*

XII. SOME FURTHER MATTERS CONSIDERED

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Judicial Comity

i. Relevance and Principles

1161. Judicial comity is an important issue in this case. So much so that I touched upon it in chapter 1, indicated that I would return to the issue later, and do so here. This chapter should be read in conjunction with what I stated in chapter 1 and that chapter should be read in conjunction with what I state here.

1162. As I mentioned in chapter 1, Ireland is neither the first nor the only jurisdiction in which the validity of the impugned patent has been challenged. Teva has been singularly unsuccessful in several jurisdictions to this time, with the notable exception of the United Kingdom. Thus, Teva has failed in France, Norway, and Sweden, all fellow parties to the European Patent Convention, applying the same law to what (on Teva's case) are the same facts. It can be very difficult to obtain English translations of foreign judgments. So for that reason I have appended to this judgment the translated versions of the French, Norwegian, and Swedish judgments that were provided to me by the parties and which I consider in detail later below.

1163. As I mentioned in chapter 1, Teva has, unsurprisingly sought to focus my attention on the reasoning of the English courts in *Sandoz Ltd* v. *BMS Holdings Ireland Unlimited Co.* [2022] EWHC 822 (Pat.) (as affirmed on appeal in [2023] EWCA Civ. 472). For obvious reasons, weight and respect falls to be accorded by me to the decisions of the neighbouring jurisdiction, not least though not only because the courts of that jurisdiction are applying the same system of patent law and both are common law jurisdictions. That said, I of course have an obligation to decide the case before me on the evidence presented to me and not on the evidence presented to any other court, whether in the United Kingdom or elsewhere. If the evidence is different the outcome may be different. As BMS has highlighted in these proceedings, among the differences between the English case and the case before me are that (i) neither of the medicinal chemists who gave evidence in London gave evidence before me, and (ii) the technical evidence before me is different. As a result, BMS maintains, the position in these proceedings is very different from that which presented, *e.g.*, in *Norton (Waterford) Ltd t/a Teva Pharmaceuticals Ireland* v. *Boehringer Ingelheim Pharma GmbH & Co. KG* [2022] IECA 58. There, the issues were being litigated with evidence from the same experts in multiple jurisdictions. By contrast, where (as here) different experts give evidence then it may well be that upon due consideration, a court will conclude that the relevant facts should be differently determined because the evidence is indeed different. In fact, I have proceeded in this judgment solely by reference to the abundant evidence before me and arrived through my own reasoning at the conclusions that I have reached as to plausibility (the courts in London were not troubled with the priority issue). So the problem that presents for BMS is that even taking the most exclusionary approach to the London proceedings, I have arrived at the same (or much the same) conclusions when it comes to the various contentions of Teva as to plausibility (and fundamentally I have arrived at the conclusion that plausibility does not present). It is true that I have at points taken comfort in the fact that Meade J. and/or Arnold L.J. have brought similar reasoning to bear to that which I have applied. However, such comfort as arises to be drawn is an ancillary consequence of my reasoning through to certain conclusions; it has played no part in the reasoning itself.

1164. While I am required by precedent to engage with parallel decisions in other jurisdictions, those precedents do not suggest that I should not determine the case on the evidence before me, rather than the evidence before the courts in other jurisdictions. In his decision in *Ranbaxy Laboratories Ltd* v. *Warner-Lambert Co* [2007] IEHC 256 , [2009] 4 I.R. 584 Clarke J., as he then was, expressly noted, at para. 4.5, that a case must be determined on the evidence presented to the deciding court. Thus, he observed, at para. 4.5:

"[B]*y way of caution, it is...appropriate to note that each case must be determined on the evidence presented to the court concerned....* [T]*hat evidence should be confined to demonstrating what the knowledge of the skilled addressee would have been as of the priority date. Given that the relevant knowledge is international it would be surprising if there were very significant differences between the conclusions which could properly be arrived at from one country to the next as to what the knowledge of the skilled addressee as of that date would have been. However, the court is, nonetheless, bound by the evidence presented to it. In that context it is worthy of some note that both Professor Clive and Dr Newton had previously given evidence in some of the other international litigation. Quite an amount of the cross-examination of both witnesses was concerned with what might be reasonably be described as suggestions of nuanced differences between the evidence now being tendered and that given on previous occasions. I have to say that such an eventuality, far from being a matter of criticism, is to be expected. The precise focus of the issues upon which a case may come to turn will undoubtedly crystallise in the course of litigation. If a second set of litigation of an almost identical variety, is then conducted with the same expert witnesses, it is hardly surprising that the legal advisors of the parties and those witnesses will focus more closely on what have turned out to be the key issues. It should not be assumed that the evidence given on the first occasion is some form of sacred text which cannot be altered. There are doubtless things that were not said because questions were not asked or issues did not arise in precisely the same way. The fact that issues may arise in a more focused way in a second or subsequent piece of litigation between the same parties is almost certain to lead to some evolution in the evidence given. That is not to say that a court would readily accept a significant alternation in the evidence given by a witness. It would require a very telling explanation to justify a witness significantly altering evidence previously given as to the state of knowledge of the skilled addressee. However, a greater focus, within that evidence, on specific questions which may not have been explored as fully in previous litigation is likely, legitimately, to lead to some nuanced evolution of the evidence given. I did not see the evidence given by either Professor Clive or Dr Newton as varying, beyond that extent, from the evidence which they had previously given. To the extent that either of the experts' evidence was criticised in that regard, I reject that criticism.*"

1165. The just-quoted paragraph, it seems to me, is notable because it shows that even where the same witnesses are giving evidence about the same matters in parallel proceedings, the evidence may evolve as the issues become more focused. *Mutatis mutandis* a like point applies with even greater rigour in a case where (as here) the deciding judge is not dealing with evidence given by the same witnesses. Notably, the key expert on both sides, the skilled medicinal chemist, is different, and it is, amongst other matters, to the evidence of the medicinal chemists who appeared before me, both learned and impressive gentlemen, that I am required to look, not at the evidence of different experts in parallel proceedings conducted elsewhere.

1166. *Ranbaxy*, being a decision of the Irish courts, is a decision well known to the Irish courts. Perhaps less well known to the Irish courts, but also helpful, is the decision of the English Court of Appeal in *E. Mishan & Sons Inc. v. Hozelock Ltd* [2020] EWCA Civ. 871. Rather than 're-invent the wheel', I will quote some of the facts of the case as stated in the reported version at [2020] RPC 19,

"*This report concerns a patent action in which the claimant ('Emson') complained of garden hoses manufactured and sold by the first defendant ('Hozelock') and which are referred to here as the 'Superhoze 1' and the 'Superhoze 2'. Emson relied on two patents, namely UK patent No. 2 490 276 ('GB 276') and European Patent (UK) No. 2 657 585 ('EP 585'), which were in similar terms and related to expandable garden*

hoses. Emson was the UK exclusive licensee under both patents ('the Patents') and marketed an embodiment of the Patents under the name 'XHose'. Hozelock denied infringement and had counterclaimed for invalidity of the Patents on grounds of obviousness...".

1167. The headnote runs at some length but the foregoing suffices to give a sense of what was in issue. Notably (and I am not aware of an Irish case in which this has occurred) the patent in suit in *Mishan* had been litigated once before in the United Kingdom and found valid over a particular item of prior art known as McDonald. The same issue was litigated in the second case and the decision was reached that the patent was obvious over McDonald. Of interest for the purposes of the present proceedings is the observation of Arnold L.J., at §4, where he states as follows:

> "*4* ....[T]*he validity and infringement of GB 276 has previously been litigated in proceedings brought against different defendants with a different outcome. In Blue Gentian LLC v Tristar Products (UK) Ltd [2013] EWHC 4098 (Pat) Birss J held that GB 276 was valid, including over McDonald, and had been infringed by the defendants. His conclusions were upheld by this Court: [2015] EWCA Civ 746. As the judge in the present case correctly noted at [40], strictly speaking the previous decisions are not admissible evidence on any question of fact arising in the present case. As he said, his function was to decide this case on the evidence adduced by parties in this case. Moreover, as he explained, the evidence in this case was materially different to that in the previous case. I shall return to this point more than once below.*"

1168. The relevance of that observation to what I have been saying thus far in this section of my judgment will be obvious.

1169. If one looks to the judgment of Clarke J. in *Ranbaxy Laboratories v Warner-Lambert* [2007] IEHC 256 and that of Collins J. in *Norton (Waterford) Ltd v Boehringer* [2022] IECA 58, two principles can be identified when it comes to judicial comity:

(1) on matters of law, the decisions of foreign courts applying the same legal rules or principles should be given persuasive effect irrespective of the factual connection between the cases.
(2) where a foreign court has determined an issue that is in dispute in litigation here the courts should not lightly depart from the decision of that foreign court.

1170. It is Principle (2) that is relevant to the case at hand. Here, as I have already mentioned, the impugned patent has been the subject of parallel proceedings in several other jurisdictions that are party to the European Patent Convention. The issues before me are therefore the same as those that went before some or all of those courts. (Priority has not been tried by all of those courts; the validity of the patent has been considered by them all).

1171. No difficulty should typically arise in applying the second principle where there is only one foreign court decision or where all foreign courts have reached the same decision for the same reasons. Where, however, there are conflicting decisions of foreign courts, the position is otherwise. If this court is to apply the principle that it should not lightly depart from a corresponding decision of a foreign court, it can do so only by engaging with the conflicting foreign decisions and determine which is or are more persuasive. The conclusion resulting from that engagement may well be that the evidence in some cases was closer to that in the case before the Irish court than that in others and that the Irish court should therefore lean towards the decision/s from courts where the evidence was more aligned with that before the Irish court.

1172. The English courts, I note, appear almost routinely to differ from their foreign counterparts

where the evidence before the English courts is different. The discussion in the United Kingdom Supreme Court in *Warner-Lambert Co. LLC* v. *Generics (UK) Ltd (t/a Mylan)* [2018] UKSC 56, [2019] 3 All E.R. 95 and in *Actavis Group PTC EHF* v. *ICOS Corporation* [2019] UKSC 15, [2020] 1 All E.R. 213, of the proper approach to be taken, was considered by the Court of Appeal in *Norton (Waterford) Ireland t/a Teva Pharmaceuticals Ltd* v. *Boehringer Ingelheim Pharma GmbH & Co. KG* [2022] IECA 58 and the conclusions reached by the United Kingdom Supreme Court adopted without criticism. Thus, per Collins J., at §§61-62:

> "*61. The issue of comity has also been considered in the specific context of EPC patent litigation by the UK Supreme Court. In* Generics UK Ltd (trading as Mylan) *v.* Warner-Lambert Co *[2018] UKSC 56...a particular claim of the patent (claim 3) was challenged as insufficient. Claim 3 had been upheld as sufficient in ligation in France, Germany and Sweden, a fact on which the patentee placed some reliance. Giving the leading judgment, Lord Sumption stated that this was:*
>
> > '[55] …. more than a forensic point. If courts in other jurisdictions have upheld Claim 3, that may serve as a reality check against my own, less favourable conclusions. Other things being equal, it would be unfortunate if different jurisdictions party to the EPC arrived at different conclusions concerning the same patent. However, other things are rarely equal, and the force of this point depends entirely on how far the factual and technical evidence before the foreign court was the same as the material before Arnold J, and how far their domestic statutes were comparable.'
>
> *Lord Sumption then addressed the decisions of those other courts and explained why they did not cause him to doubt the conclusions he had reached as a matter of English law, in light of the evidence given and the facts found in the proceedings (at paras 56-60).*
>
> *62. The issue was also addressed by the Supreme Court (per Lord Hodge) in* Actavis Group PTC *v.* ICOS Corporation *[2019] UKSC 15, [2020] 1 All ER 213. The issue there was whether the claims in a dosage patent were obvious. The issue had been the subject of litigation in a significant number of EPC States, with different views being reached on the issue of obviousness. Lord Hodge began by observing that* 'while consistency of approach between the domestic courts of the signatory states to the EPC on matters of principle is desirable, we are not bound by the judgments of other national courts and it is possible that national courts applying the same law may come to different conclusions for a various reasons' *(para 97). Lord Hodge then briefly addressed the decisions particularly relied on by the claimants and commented that one* 'can draw some support from judicial decisions in other national courts which reach the same conclusions as one has come to. But it is necessary to recognise not only that the first instance decisions in the Netherlands and Germany are the subject of appeals but also that the evidence led before the different courts may differ and, even when the same evidence is led, each court's findings of fact based on that evidence may not be the same' *(para 100). Having referred to some of the findings made in the Netherlands and Germany and how they differed from the findings made in the English proceedings, Lord Hodge concluded in the following terms:*
>
> > '[101] Because of the differences in the evidence led, the manner by which it is tested, and the differing findings to which

> that evidence gives rise, one may derive support from the approach to the question and the methods of reasoning of other national courts but should never rely uncritically on the outcome.'"

1173. A further recent decision of interest in this regard, to which I have been referred by counsel for BMS, is that of the English Court of Appeal in *Advanced Bionics AG, Advanced Bionics UK Limited* v. *Med-El Elektromedizinische Geräte GmbH* [2023] EWCA Civ 637. There, the appellant was the owner of a patent that claimed a cochlear implant that comprised a magnet that made the implant safer in MRI scans. (A cochlear implant is a small electronic device that assists a person who is profoundly deaf or hard of hearing). The trial judge dismissed the claim of validity, holding that the patent was obvious because of the prior art. The Court of Appeal, dismissed the appeal from this decision, holding that the trial judge had been correct to find that the appellant's patent for a cochlear implant was obvious over prior art in regard to its ability to be safe in MRI scans. In the course of his judgment, Arnold L.J. observed as follows, at §96:

> "*The final point to mention is that Med-El relied upon the decision of the Board of Appeal that the Patent was not obvious over Zimmerling as lending support to their case that the judge had erred. This does not follow. It* [is] *often possible for two tribunals faced with a finely-balanced issue as to obviousness to reach opposing conclusions without either tribunal making an error. In the present case, the Board of Appeal did not have the evidence of the expert witnesses as to the common general knowledge which was before the judge. For example, there is no mention in the Board's decision of the fact that it was common general knowledge that a diametrically magnetised magnet can be rotated by an external magnetic field. Nor is there any discussion of the reasons accepted by the judge as to why, based on their common general knowledge, the skilled team would want, if possible, to retain the conventional disc-shaped internal magnet. Thus the fact that the Board reached a different conclusion is more than sufficiently explained by the fact that it did not have the same evidence as the judge.*"

1174. What principles concerning judicial comity (with a particular emphasis on patent law proceedings) can be gleaned from the foregoing consideration of case-law? It seems to me that the following might safely be stated:

[1] In matters of patent law, weight and respect falls to be accorded to the decisions of the United Kingdom courts, not least though not only because the courts of the United Kingdom are applying the same system of patent law and both are common law jurisdictions.

[2] Notwithstanding [1], a case must be determined on the evidence presented to the deciding court. Thus, an Irish court has an obligation to decide the case before it on the evidence presented to it and not on the evidence presented to any other court, whether in the United Kingdom or elsewhere. If the evidence is different, the outcome may be different.

[3] Even where the same witnesses are giving evidence about the same matters in parallel proceedings, the evidence may evolve as the issues become more focused. *Mutatis mutandis* the same applies with even greater rigour in a case where (as here) the deciding judge is not dealing with evidence given by the same witnesses.

[4] Where the relevant knowledge is international it would be surprising if there were very significant differences between the conclusions which could properly be arrived at from one country to the next as to what the knowledge of the skilled addressee as of a particular date would have been. However, the Irish court is, nonetheless, bound by the evidence presented to it.

[5] Notwithstanding [4]. it should not be assumed that the evidence given on the

first occasion is some form of sacred text which cannot be altered. There are doubtless things that were not said because questions were not asked or issues did not arise in precisely the same way. The fact that issues may arise in a more focused way in a second or subsequent piece of litigation between the same parties is almost certain to lead to some evolution in the evidence given.

[6] Notwithstanding [5], a court may not readily accept a significant alteration in the evidence given by a witness. It would require a very telling explanation to justify a witness significantly altering evidence previously given as to the state of knowledge of the skilled addressee.

[7] Further to [6], a greater focus, within such evidence, on specific questions which may not have been explored as fully in previous litigation is likely, legitimately, to lead to some nuanced evolution of the evidence given.

[8] Even where the same issue is being litigated in a second patent case, strictly speaking the previous decision is not admissible evidence on any question of fact arising in the second case.

[9] On matters of law the decisions of foreign courts applying the same legal rules or principles should be given persuasive effect irrespective of the factual connection between the cases.

[10] Where a foreign court has determined an issue that is in dispute in litigation before an Irish court the courts should not lightly depart from the decision of that foreign court.

[11] No difficulty should typically arise in applying [10] where there is only one foreign court decision or where all foreign courts have reached the same decision for the same reasons.

[12] Where there are conflicting decisions of foreign courts, the position is otherwise. If an Irish court is to apply the principle that it should not lightly depart from a corresponding decision of a foreign court, it can do so only by engaging with the conflicting foreign decisions and determine which is or are more persuasive. The conclusion resulting from that engagement may well be that the evidence in some cases was closer to that in the case before the Irish court than that in others and therefore the Irish court should therefore lean towards the decision/s from courts where the evidence was more aligned with the evidence before the Irish court.

[13] Where in patent litigation brought in the courts of another state that is party to the European Patent Convention a claim has been upheld as sufficient, that may serve as a reality check against an Irish court reaching less favourable conclusions.

[14] Other things being equal, it would be unfortunate if the courts of different jurisdictions that are party to the European Patent Convention arrived at different conclusions concerning the same patent.

[15] Further to [14], other things are rarely equal, and the force of [14] depends entirely on how far the factual and technical evidence before the foreign court is the same as the material before the Irish court and how far their domestic statutes are comparable. (I note in passing that the Irish and British statutes concerning patent law are singularly comparable; however, regard it seems to me can also be had to whether a decision of the English courts represents something of an outlier in terms of the trend of decisions among the courts of successive European Patent Convention countries in a sequence of parallel proceedings).

[16] While consistency of approach between the domestic courts of the signatory states to the European Patent Convention on matters of principle is desirable, the courts of Ireland are not bound by the judgments of other national courts and it is possible that national courts applying the same law may come to different conclusions for various reasons.

[17] Even when the same evidence is led, the findings of fact by the courts of different jurisdictions based on the same evidence may not be the same.

[18] Because of differences in evidence led, the manner by which it is tested, and the differing findings to which that evidence gives rise, an Irish court may derive support from the approach to the question and the methods of reasoning of other national courts but should never rely uncritically on the outcome.

[19] It is often possible for two tribunals faced with a finely balanced issue as to obviousness to reach opposing conclusions without either tribunal making an error.

1175. Returning to the principle that where a foreign court has determined an issue that is in dispute in litigation before an Irish court, the Irish courts should not lightly depart from the decision of the foreign court, the difficulty in applying the principle in this case is that there is not any uniformity of decision-making in the foreign courts.

ii. The Trial Court Decision in London

Sandoz Ltd v. *BMS Holdings Ireland Unlimited Co.*
[2022] EWHC 822 (Pat.),
(affirmed on appeal in [2023] EWCA Civ. 472)

1176. As I have already pointed out, all final decisions that have thus far been rendered by the courts of contracting states to the European Patent Convention have been in favour of BMS, the sole exception to this trend being the courts of the United Kingdom. Yet it is the decision in the United Kingdom which Teva has strongly contended should be adopted by me, contending that the decision of the English courts represents the next best thing to issue estoppel. In this regard, I recall the following observations of counsel for Teva in his opening submissions:

> "*Now, I'm not saying that an issue estoppel arises* [counsel could not say this because an issue estoppel does not actually arise], *but I do say the Court should look very carefully at any attempt to alter the case or alter the presentation to this Court.*
>
> ...
>
> *I am not relying on an issue estoppel* [again, counsel could not rely on issue estoppel because it does not present], *but I'm saying it would require some extraordinary justification, or very clear justification at the very least, to justify that approach.*"

1177. Extracted so, the just-quoted observations lose their context. However, essentially the point being made in this regard by counsel for Teva was that the decision in the United Kingdom should be adopted by me, almost (though not, I think, quite) without consideration of the merits of each side's case on the evidence before me. As can be seen from the quoted observations, it was effectively being contended that Meade J.'s findings of fact were determinative of the issues before this court.

1178. For me to adopt such an approach would be wrong in principle for the reasons set out previously above. Before I could properly adopt the decision of Meade J., I would have to be satisfied that the evidence before me and before the English High Court was the same. That I cannot do. In this regard, I note the following in particular:

- the evidence before me as to the teaching of the specification of the application differs from the evidence before Meade J. in the United Kingdom.

- when one examines Meade J.'s judgment, and in particular the passages that were read out to me by counsel for Teva during his opening, it appears that the case advanced in London depended largely on the claims of efficacy made in the application, rather than the analysis which has been presented before me based on the molecules which are found in embodiment 8 and the synthesised examples.
- the evidence before Meade J. about what such structural analysis involved seems to have been different from the evidence before me. Here, Dr Young (called by BMS) has explained that to a medicinal chemist the task of analysing the compounds in these groups is straightforward and Dr Edwards (called by Teva) accepted that it could be done. This seems to be a key distinction from the evidence in London. There, Dr Redshaw (called by Teva/Sandoz) gave evidence that it was not practically possible to obtain the structures of the molecules from their IUPAC names. And Dr Camp (called by BMS), having originally given evidence that it was practically possible, retreated from his written evidence, saying that it was not the sort of analysis which a medicinal chemist would have carried out without biological data.
- great emphasis was placed before Meade J on the fact that 3g of Example 18 was made. Before me, the quantity made has been proffered by BMS (as I understand its closing submissions) as but an *additional* crutch on which to rest a finding of plausibility.
- by contrast to the evidence before Meade J, the experts are agreed here that balancing the potency, selectivity and biological properties of a molecule is a key part of optimising its properties and that higher bioavailability may make up for lower potency as noted above. The evidence before Meade J., I understand, was to the opposite effect.

1179. All that said, I did consider that BMS went somewhat overboard in emphasising the differences between the English case and the case before me. At all times it sounded a little strange to me that when the same patent was in issue, the same issue (plausibility) was in issue, and a similar legal system was being brought to bear in a fellow common law country in proceedings involving the same parties (albeit somewhat different independent expert witnesses) that the evidence would be wildly different. In this regard, I respectfully adopt the following observations of Teva in its closing submissions as to the similarities between what transpired in London and before me:

> "*220. The cgk in these proceedings is underpinned by the Statement of Agreed CGK which was annexed to the end of Meade J's judgment. So far as BMS seeks to point to different witnesses to suggest a different evidential record, much of that is answered by the common Statement of Agreed CGK in which, notably, references are given to the evidence in the expert reports before the UK court.*
>
> *220. Two of BMS's three witnesses were the same individuals as in the UK. Professor Morrissey was not called in these proceedings but his written and oral evidence from the UK was admitted....Professor Taft entered reports in both proceedings which provided substantively similar content, and BMS did not suggest there were any (nor any material) differences as far as pharmacokinetic evidence was concerned.*
>
> *221. BMS has switched...for its medicinal chemistry evidence, from Dr Camp to Dr Young. As we have noted, much of Dr Camp's evidence has been incorporated via the Agreed CGK. Further:*
>
> a. *Dr Young admitted in his direct examination that the cgk materials upon which he had based his report (namely, the contemporaneous literature) had been provided to him by...Wilmer Hale, the US-based firm which is coordinating BMS's case across*

jurisdictions)....It further emerged in evidence that every item of literature listed by Dr Young in his second witness statement was actually the product of Dr Camp's searches. Therefore, the foundation of Dr Young's report is the same as that in the English evidence.

b. ...[There is] *near identity of substance and sequence between Dr Young's central conclusions in Young 1 paragraph 77 and those of Dr Camp in Camp I paragraph 11.2-11.8.*

c. *The compounds...identified by Dr Young as being part of the CGK are substantially the same as those identified by Dr Camp*".

1180. Just as I thought that BMS went somewhat overboard in emphasising the *differences* between the English case and the case before me, I also thought that Teva went somewhat overboard in emphasising the similarities. One can start with the same foundational documents but that does not mean that the end-evidence will in all respects be similar. And we had days of oral testimony in these proceedings with the examination, cross-examination, and re-examination being undertaken by different counsel from those who acted in London, touching in different ways upon often similar points and receiving answers that just could not have matched in every respect, including the language used, what was stated in London. What presents then is a case fought in two very similar jurisdictions with the same fundamental issue (plausibility) in issue and sometimes similar, sometimes dissimilar evidence in play. In such a situation, what is a judge to do?

1181. As mentioned above, I have proceeded in this judgment solely by reference to the abundant evidence before me and arrived through my own reasoning at the conclusions that I have reached as to plausibility (the courts in London were not troubled with the priority issue). So the problem that presents for Teva is that even taking the most exclusionary approach to the London proceedings, I have arrived at the same (or much the same) conclusions when it comes to the various contentions of BMS as to plausibility (and fundamentally I have arrived at the conclusion that plausibility does not present). It is true that I have at points taken comfort in the fact that Meade J. and/or Arnold L.J. have brought similar reasoning to bear to that which I have applied. However, such comfort as arises to be drawn is an ancillary consequence of my reasoning through to certain conclusions; it has played no part in the reasoning itself.

iii. The Trial Court Decision in Oslo

Teva Norway AS and Anor v. *BMS Holdings Ireland Unlimited Company*,
Oslo District Court, 22nd May 2023.

1182. An English-language translation of this judgment is set out in Appendix 18. Pages 17-29 are key in terms of understanding the court's reasons for concluding that on the basis of the disclosure in the application apixaban is a plausible factor Xa inhibitor. The following aspects of the Oslo decision might usefully be noted:

- the court assesses the disclosure on the basis of the application with the CGK in mind, observing in this regard (at p.20), that "*The assessment as to whether the invention in NO558 has an inventive step shall be made on the basis of the patent application on which the invention was based, i.e. WO652. The question is what can be derived therefrom, having common general knowledge in mind*".
- the court noted that (oddly perhaps given that this was to become the subject of dispute before me) (p.21) "*The parties essentially agree*[d] [my emphasis] *on the skilled person in the present case. The Court will proceed on the basis that the skilled person is a team with knowledge of factor Xa inhibitors and expertise*

in medicinal chemistry, biology/biochemistry, pharmacology, pharmacokinetics, safety and clinical medicine". If nothing else this may suggest why, notwithstanding the approach adopted in the United Kingdom, BMS saw fit to contend before me that the skilled team would include a skilled pharmacokineticist (and clearly considered it appropriate so to contend).

- as in the case before me there was an agreed CGK document before the Oslo Court which, as I read p.21 of the judgment, was (as before me) the agreed CGK document from London.
- the Oslo court identified that:

  – (at 21) "*the disagreement between the parties relates to how the skilled team would have read/understood the patent application based on common general knowledge in the art*";
  – (at 22) "*DX-9065a was an early potent factor Xa inhibitor, but did not have the desired drug-like properties, primarily due to poor bioavailability. The reason for this was that the molecule is charged at physiological pH. The charge comes from the strongly basic amidine groups*";
  – (at 23) "*A next step in the development can be represented by DPC-423....one of the most important advances in the search for oral factor Xa inhibitors….*";
  – (at 23) "*WO131 builds on compound DPC 423. WO131 pertains to factor Xa inhibitors with a bicyclic nitrogen-containing core composed of a 5-- ring and a 5-7 ring*";
  – (at 24) "*A comparison of DPC423 with WO131 shows that a step-by-step optimisation has taken place....The skilled person will recognise that the structure of DPC-423 is rigidified through a cyclisation in the centre of the molecule, while a weakly basic benzyl group in P1 is retained*";
  – (at 24) "*…both DPC 423 and WO 131 are precursors to the development of apixaban*",

- taking a problem-solution approach to the assessment of inventive step, the Oslo court identified that:

  – (at 25) the court proceeded "*on the basis that a technical problem the invention aimed to solve was to provide an effective factor Xa inhibitor with improved properties for the treatment of thromboembolic disorders….*"
  – (at 24) "*…the closest prior art, which would have constituted the most promising starting point for a development leading to the invention, is WO131….*"
  – (at 25-26), assessing the issue of whether the patent application made a contribution to the state of the art, the court observed as follows:

    "*Teva has argued that it does not appear plausible that a contribution to the state of the art has been provided through the patent application. Teva's line of argument is as follows. The application disclosed a general Markush formula comprising a very large number of potential chemical compounds, only a few of which had been synthesised, and 140 specific compounds are included in the example section.*

Without biological data that substantiate efficacy, it is not plausible to the skilled person, as at the application date, that the compounds, including apixaban, are potentially useful factor Xa inhibitors. The Court does not agree with this."

A detailed explanation for this disagreement then follows, including the following observations at p.26:

"*In the understanding of the Court the issue before it is that of whether apixaban solves the problem at which the invention is aimed. The Court is of the view that this is not a matter of plausibility for all compounds in the application, as claimed by Teva. The Court refers to T488/17 (Dasatinib), paragraph 4.2...where it is stated that the assessment pertains to the 'claimed subject matter'. The disputed application in Dasatinib concerned a large number of compounds encompassed by a Markush formula (like the application in the present case) with 580b compounds, including Dasatinib. The following is quoted from that ruling (emphasis added by the Court):*

> *'It is established jurisprudence of the boards of appeal that the assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common general knowledge then available to the skilled person. Post-published evidence in support that the claimed subject-matter solves the technical problem the patent in suit purports to solve may be taken into consideration., if it is already plausible from the disclosure of the patent that the problem is indeed solved....*
>
> *Thus, for post-published evidence to be taken into account, it is necessary to establish whether or not the asserted activity has been made sufficiently plausible for dasatinib at the effective date of the patent in suit....*[The] *basis for this assessment is the application as filed and the common general knowledge of the person skilled in the art at the filing date.'*

Consequently, the Court's assessment as to whether the inventive step requirement is met only encompasses apixaban, and not all the other compounds in the patent application."

- Dr Young, I note, gave evidence in Oslo that appears from what I can see in the judgment of the Oslo court to have been much the same evidence that he gave before me (though what is expressly identified as having been stated by Dr Young is limited).
- at pp.27-29 the Oslo court indicates its view that the skilled person/skilled team would have made the assessment it identifies of the patent application, having common general knowledge in mind. The reasoning is in or about 2+ pages long but well worth the read. As the full judgment is set out in Appendix 18, I would simply refer the reader to the text that appears from paragraph 3 on p.27 ("*Based on the evidence presented...*") to the end of paragraph 5 on p.29 ("*...the skilled person would have considered apixaban to be a plausibly effective factor Xa inhibitor*").

1183. Notwithstanding the foregoing, I respectfully do not consider that the Norwegian judgment can safely be followed by me. There are a few reasons why this is so. First, the judgment does not rely on Norwegian case-law but on a Norwegian textbook on patent law in which plausibility is described by reference to case-law that precedes *Warner-Lambert* by seven years (and so also pre-dates *Boehringer)*. Second, the court in Norway peremptorily dismisses the relevance of the decision of the English Court of Appeal in *Sandoz Ltd* v. *BMS Holdings Ireland Unlimited Co.* Such an approach sits askew with the approach adopted by the courts of Ireland when it comes to comity with decisions of the courts of England and Wales.

1184. I have noted previously above, and I ought perhaps to note again before ending this chapter that in his closing oral submissions, counsel for Teva made an unexpected proposition as to plausibility. Thus he suggested that Norway does not have the same law of plausibility as Ireland and the UK as one of the reasons why I should not give the same weight to a decision in Norway as to a decision in the UK. It may have been a slip of the tongue: the legal team for Teva was so distinguished that I half-suspect it was. However, I must respectfully note that it is a mistaken proposition. Plausibility is a concept which has been created under the European Patent Convention. It was developed by the tribunals of the European Patent Office, the jurisprudence of which applies equally in all states that are contracting parties to the European Patent Convention. The idea that the law in Norway is any different in relation to plausibility than the law here and the law in the United Kingdom is not only unarguable, it is, with every respect, wrong.

iv. The Trial Court Decision in Paris

S.A.S. Teva Santé v. *BMS Holdings Ireland Unlimited Company*
(Judicial Court of Paris, 8th June 2023)

1185. An English-language translation of this judgment is set out in Appendix 17. It is a denser read than the Norwegian judgment but effectively proceeds as indicated hereafter. Thus, the court:

- identifies the underlying facts and summarises the disclosure of the patent in suit (see §§1-33).
- addresses obviousness, Teva again arguing (§35) that lack of test data vitiated the patent.
- identifies in the following terms (at §47) the person skilled in the art, being "*a multidisciplinary team consisting of a medicinal chemist, a pharmacologist, a pharmacokineticist, and a physician experienced in anticoagulants*". If nothing else this may suggest why, notwithstanding the approach adopted in the United Kingdom, BMS saw fit to contend before me that the skilled team would include a skilled pharmacokineticist (and clearly considered it appropriate so to contend).
- makes the following comments as to plausibility, at §§48-51:

"*48. As further rightly recalled by BMS, French case-law does not require the patentees to demonstrate, through testing or disclosure of data that would appear in the patent, the claimed technical effect, except in the case of patents referred to as second therapeutic application* [which was not the case in Paris or before me].

49. In this case, the invention relating to the new therapeutic application of a known product, it is expected of the patentee to describe through tests, in particular, this new effect claimed, for the purpose that the person skilled in the art understands the invention and that the invention is viewed as 'plausible' (and sufficiently described): 'Where a claim relates to a subsequent therapeutic application of a substance or composition, obtaining that therapeutic effect is a functional technical characteristic of the claim, so that if, in order to meet the requirement of sufficiency of disclosure, it is not necessary to clinically demonstrate this therapeutic effect, however the patent application must directly and unambiguously reflect the therapeutic application claimed, so that the person skilled in the art understands, based on commonly accepted models, that the results reflect this therapeutic application….

50. This requirement does not exist for other patents that normally cover a new product regardless of its therapeutic application (which is the case here of claims 1-6).

51. However, case law does not consider as valid a patent which, from the point of view of the person skilled in the art, would not make any contribution to the state of the art or which would allow its applicant to reserve a field of research that has not yet made concrete and technical results. An invention must therefore have a 'credible' or 'plausible' technical effect at the filing date, the absence of which is sanctioned in the ground of lack of inventive step (see for example TGI Parios, 6th October 2009, RG no 07/16446 Teva/Sepracor) The credible nature of the technical effect is assessed at the priority or filing date (e.g. TGI Paris, 6 October 2009, RG no. 07/16446, Teva/Sepracor), in view of the elements contained in the application, including the patent claims, without the latter being obliged to provide the results of tests or trials or any other data (see for example CA Paris, 29th October 2020, RG no. 126/2019, Ethypharm/Merck Sharpe & Dohme Corp). Post-filing elements may also be considered but cannot be used as a single basis for demonstrating credibility of the technical effect (e.g., TGI Paris, 6th October 2009, RG no 07/16446, Teva/Sepracor)."

- notable too is §55 where (as with the Oslo court), the Paris court identifies that the most preferred compounds had nanomolar potency and takes heed also of the amount of apixaban which was synthesised.

- at §63, the Paris Court rejects the notion that 652 does not make apixaban plausible, and at §§64-69 it rejects the allegation of lack of inventive step (obviousness over WO131) on the basis that there is no incentive offered by WO131 to make the necessary selections from its broad disclosure to arrive at Example 18 of 652.
- at §§70-88 the Paris Court considers and rejects the priority attack which has been advanced before me. Those paragraphs extend over about five pages and are too long to quote here; however, they reward reading and are set out in Appendix 17.
- at §§89-94, the court addresses the issue of insufficiency of disclosure (based on lack of plausibility) rejecting this argument essentially for the same reasons which led it to reject the obviousness case.

1186. Notwithstanding the foregoing, I respectfully do not consider that the French judgment can safely be followed by me. The French decision is expressly premised on data which is not contained within the Application. Thus, the French court refers to data which was submitted by BMS and demonstrated the efficacy of apixaban. None of that data is present in the application. On that basis, the French court decided that the application was credible. That approach is at odds with the understanding of plausibility in Ireland. The issue of whether or not the invention works in fact is an allegation of classical (in)sufficiency. That allegation has not been pursued in the proceedings before me.

v. The Trial Court Decision in Stockholm
Teva Sweden Aktiebolag v. *BMS Holdings Ireland Unlimited Company*,
2nd November 2022

1187. An English-language translation of this judgment is set out in Appendix 19. The following points might usefully be noted from the judgment:

[1] the Stockholm court turns to the issue of novelty at p.23. After an analysis of the issues raised, the Stockholm court, at p.29, rejects the argument that BMS is not entitled to priority. The analysis is about seven pages, and is too long to quote here; however, it rewards reading.

[2] at p.30 the Stockholm court turns to the issue of inventive step. As in the case before me, the cited prior art is WO131. The court notes the differences between WO131 and apixaban. At pp.30-31 it concludes that the skilled addressee would not on the basis of what is disclosed in WO131 arrive at the apixaban molecule.

[3] The Stockholm court turns next to Teva's claim as to plausibility. (There is, with respect, a mistranslation in the very readable translation produced by the Swedish-to-English translator text whereby what is 'plausible' is referred to as what is 'probable' but it is clearly 'plausibility' that was the issue raised). In this regard, the court sets out the background to the patent, identifies that the preferred potency levels are in the nanomolar range, then treats with the common general knowledge (identifying the coagulation cascade and the binding sites of factor Xa), refers to Maignan and Mikol, refers to Dr Gallagher's evidence (he also gave evidence in Sweden) that a skilled person was aware of the requirements for a potentially useful factor Xa inhibitor) and (at p.34) notes as follows:

> "*The Court notes that the Patent describes experiments that have been carried out, but that there is no mention of specific biological data. However, in practice, there is no absolute requirement that experimental data be disclosed in a patent (or in a patent application). In some cases, a mechanistic*

explanation or the general knowledge of a person skilled in the art may be sufficient (see EPO Technical Board of Appeal decisions in T-578/06 and T1322/17...)."

[In Case T-578/06 *Pancreatic cells /IPSEN* (ECLI:EP:BA:2011:T057806.20110629), the examining division refused the application for a European patent on the ground that the subject-matter of the claims before it lacked inventive step. The appellant brought a successful appeal against this decision. For present purposes it suffices to note that, in its reasoning, the Technical Board of Appeal (chaired by Mr Rennie-Smith, one of the witnesses before me) observes in its decision, at §13 that:

> "[T]*he EPC requires no experimental proof for patentability and considers that the disclosure of experimental data or results in the application as filed and/or post-published evidence is not always required to establish that the claimed subject-matter solves the objective technical problem. This is in particular true in the absence of any formulated substantiated doubt as is the case here.*"

In Case T-1322/17 *Ibandronate/ATNAHS* (ECLI:EP:BA:2019:T132217.20190319), the Technical Board of Appeal was dealing with appeals from the decision of the opposition division to reject certain oppositions. For present purposes it suffices to note that, in its reasoning, the Technical Board of Appeal observes in its decision, at §4.4.3 that:

> "…[A]*s a matter of principle experimental evidence is not limited to clinical data. It is up to the parties, which evidence they consider appropriate for substantiating a certain fact. It is also noted that experimental evidence is not always necessary to render a certain effect plausible. A mechanistic explanation and/or common general knowledge may be sufficient in certain instances.*"].

[4] at p.35 the Stockholm court concludes that:

> "*A person skilled in the art, recognising that apixaban was an fXa inhibitor, would have realised its potential suitability in connection with the treatment of thromboembolic disorders. This could have been confirmed via the routine experiments specified in the patent specification*".

[5] a reading of the judgment suggests that the Stockholm Court had before it technical evidence similar, at least in some respects, to that which has been presented before me.

1188. Notwithstanding the foregoing, I do not consider that the Swedish judgment can safely be followed by me. There are a few reasons why this is so. First, some of the Swedish judgment is

concerned with classical obviousness which was not a ground advanced before me. Second, the Swedish court identifies no authority or case-law when determining the standard of plausibility but (on p.30) suggests that "[T]*he technical effect must be possible to derive from the patent application either directly or via the skilled person's general knowledge*". Being "*possible to derive*" is not the *Boehringer* test which requires real reason to be shown. Third, at a later operative stage of its judgment the Swedish court refers to there being "*no reason to doubt*" the invention, so neither in the test as to plausibility nor in the application of that test does the court proceed in a manner similar to that which the courts of Ireland adopt.

vi. The Dutch Decision Latterly Received

1189. On 8th September 2023, after I reserved judgment in this case, I was provided with a very recent judgment of the Court of Appeal of The Hague in *BMS Holdings Ireland Unlimited Co* v. *Sandoz BV and ors* (Decision of 15th August 2023). Because it can be difficult to obtain English language translations of foreign language judgments, I have included the text of that judgment in Appendix 21.

1190. In its judgment the Court of Appeal of The Hague reverses a decision of the District Court refusing relief in preliminary court proceedings. Immediately, I observe that these were preliminary proceedings only. That noted, among its conclusions the Court of Appeal states (at §6.34) that it "*does not see any reason on the basis of Sandoz et al.'s arguments to assume in advance that the outcome of the French and Norwegian proceedings on the merits would be incorrect*". The Court of Appeal of The Hague also takes issue with the legal test applied by the High Court and the Court of Appeal in England and Wales, noting that both courts are bound by the decision of the UK Supreme Court in *Warner-Lambert* (see §§6.27-6.28).

1191. I have already indicated above the position that I consider to present (i) *vis-à-vis* the French, Norwegian, and Swedish decisions, and (ii) as regards the significance of the judgments of the English High Court and the Court of Appeal. I have also had due regard amongst other matters to the decision of the Irish Court of Appeal in *Boehringer*, a decision that is of course binding on me. Respectfully, I see nothing in the decision of the Court of Appeal of The Hague that would cause me to alter the conclusions that I have otherwise arrived at in this judgment. I am, however, grateful to counsel for sending me the text of the judgment of the Court of Appeal of The Hague.

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The Expert Evidence

i. Some Case-Law

1192. Criticism has been raised by Teva regarding the manner in which BMS has instructed its expert witnesses in this case. There is no merit to these criticisms. However, the matter having been raised, I must address it. I have been referred in this regard to, and have considered, (i) O.39, rr.57(1) and 58(1) RSC and (ii) to the observations (a) of Creswell J. in *The Ikarian Reefer* [1993] 2 Lloyd's Rep. 68, (b) MacMenamin J. in *O'Leary* v. *Mercy University Hospital Cork Limited and anor*[2019] IESC 48,[2019] 2 IR 478 §§40 and 44, (c) Collins J. in *Duffy* v. *McGee* [2022] IECA 254, at §§5, 19-21 (including footnote 5), 23, and 26, (c) myself in *Re Boehringer Ingelheim Pharma GmbH* [2017] IEHC 495 (where I touched upon the issue of hindsight, at §204), and Meade J. in *Fisher & Paykel Healthcare Limited v. Flexicare Medical Limited* [2020] EWHC 3282 (Pat), at §§19-21 and 23-26, where hindsight is comprehensively addressed. (I should note in passing that BMS conducted these proceedings by focusing on the debate between experts where there was a material issue in dispute.)

1193. One case not mentioned by Teva but which was referred to by BMS and which I consider can usefully be considered when it comes to expert evidence in patent law proceedings is the decision of the English High Court (Arnold J.) in *Medimmune Limited* v. *Novartis* [2011] EWHC 1669 (Pat.), a case which highlights the longstanding recognition in English law that close co-operation between the lawyers and an expert in patent litigation is inevitable. Given that (i) the duties of an expert witness in Ireland and England are identical, and (ii) the role of an expert in a patent case is necessarily the same, it seems to me that the approach adopted by the English courts in this regard is equally applicable in Ireland. In *Medimmune*, just before embarking on a consideration of certain aspects of the expert evidence before him and certain submissions in relation to same, Arnold J., as he then was, embarked on something of an excursus on the role of expert witnesses in patent litigation, in the course of which he stated as follows, in terms that I respectfully adopt:

> "*[109] Expert witnesses in patent litigation stand in a rather unusual position. They are generally leading scientists or engineers in the field in question. Frequently they are academics. Sometimes they are consultants. In most cases, they will not have given expert evidence in patent litigation before, although there are exceptions to this. Not only that, but also they will generally have little experience of the patent system. Where do they have experience, it will generally be as inventors named on patents. As such, they may have had scientific input, but generally they will have learnt little about patent law in the process. In some fields, they may also be accustomed to using patents and patent applications as sources of technical information, but again without necessarily understanding much about patents themselves. When asked to prepare an expert report in a patent case, they will have to consider such questions as the identity and attributes of the person skilled in the art to whom the patent is addressed, the common general knowledge of the skilled person and whether something would or would not be obvious to that person in the light of particular prior art given the constraints imposed by the law of obviousness. Usually, this is not a task of which they will have any previous experience.*
>
> *[110] For these reasons expert witnesses in patent actions require a high level of instruction by the lawyers. Furthermore, even if they are experienced authors, they need considerable assistance from the lawyers in drafting their report. In practice, most expert reports in patent cases are drafted by the lawyers on the basis of what the expert has told them and the draft is then*

amended by the expert. This, of course, requires the lawyers to understand what the expert is saying. It follows that the drafting of an expert's report in a patent action involves a steep learning curve for both the expert and the lawyers. The lawyers are learning the technology and the expert is learning enough of the law to understand the questions he must address. It follows that a high degree of consultation between the expert and the lawyers is required. Frequently, the preparation of the report will involve an iterative process through a number of drafts.

[111] It is obvious that this process entails a risk of loss of objectivity on the part of the expert even if the expert is striving to remain independent and impartial. It is therefore crucial that the lawyers involved should keep the expert's need to remain objective at the forefront of their minds at all times. If they cause or allow the expert to lose his objectivity, they are doing both the expert and their client a disservice. They are doing the expert a disservice because he may be subject to criticism during cross-examination and in the court's judgment as a result. They are doing the client a disservice because partisan expert evidence is almost always exposed as such in cross-examination, which is likely to reduce, if not eliminate, the value of the evidence to the client's case."

1194. Just while treating with *Medimmune*, I should perhaps mention that – while I do not recall that this was ever expressly posited – it did seem to me (and certainly BMS, in its closing written submissions, indicates that it too took this to be the case) that, when it came to Teva's submissions regarding Dr Young's evidence, what was essentially being contested was that BMS's lawyers failed to ensure that they did not keep the expert's need to remain objective at the forefront of their minds at all times, with the result that they undermined the expert's impartiality in the course of their instruction and assistance. There is no evidence before me which offers a proper basis for me so to conclude.

ii. Order 39, rule 57(1), RSC

1195. As to O.39, r.57(1) RSC, each expert report filed by BMS in this case complies with the Rules of the Superior Courts and contains a statement acknowledging the duty mentioned in O.39, r.57(1). There is no evidence that any of the BMS experts did not comply with their central obligation of providing independent and unbiased expert evidence.

iii. The Pharmacokinetic Evidence

1196. Teva maintains that BMS's leading the evidence of a pharmacokineticist "*unavoidably led*" Teva to proffering its own expert in this regard, despite the pharmacokinetic evidence being "*obviously irrelevant*". Two points might be made in this regard:

- first, there is, it seems to me, a touch of 'having one's cake and eating it' about Teva's contentions in this regard. If (a) the evidence was (per Teva) so "*obviously irrelevant*", then what true need was there for Teva to proffer a pharmacokineticist as an expert witness, but if (b) Teva perceived there to be a true need to proffer a pharmacokineticist as an expert witness, then can it truly be said that the pharmacokinetic evidence was so "*obviously irrelevant*"? (Of course if no pharmacokinetic evidence was proffered by Teva, then BMS's pharmacokinetic evidence would be uncontradicted, but uncontradicted evidence that is "*obviously irrelevant*" remains "*obviously irrelevant*", even if uncontradicted.)
- second, although indemnity costs were awarded against BMS in the United Kingdom for having led the pharmacokinetic evidence, it seems to me that BMS and its lawyers are perfectly entitled to disagree with the conclusions of the English High Court and to maintain in later parallel but separate proceedings in Ireland that pharmacokinetic evidence *is* relevant. As it happens, I have concluded that the skilled

team comprises a skilled medicinal chemist and a skilled pharmacologist. However, BMS may disagree with me on this point and may appeal my finding to the Court of Appeal, which may or may not agree with BMS. I see nothing inappropriate in this.

1197. As to the related contention that BMS's leading the evidence of a pharmacokineticist falls "*firmly foul*" of O.39, r.58(1), I do not see that this is so. That rule states that "*Expert evidence shall be restricted to that which is reasonably required to enable the court to determine the proceedings*". If, as BMS clearly believes, the skilled team would include a skilled pharmacokineticist, then I do not see how it could *not* have included a pharmacokineticist among its expert witnesses.

iv. The Credibility and Independence of BMS's Expert Witnesses

a. General

1198. Turning to Teva's attack on the credibility and independence of the expert witnesses called by BMS in these proceedings, I respectfully adopt as correct the proposition canvassed for by BMS in its written closing submissions, namely that such a line of attack "*is rarely done and then only where a clear case to that effect can be made out. There was simply no basis for any such attack here...*[and] *it is noteworthy that this has not happened in any other jurisdiction.*"

1199. It is not entirely clear to me why persons who have given evidence as expert witnesses in parallel proceedings in other jurisdictions and not been assailed there on grounds of credibility and independence, would fall to be treated in a different manner when giving evidence in Ireland. Be that as it may, Teva has clearly concluded that this *is* a case where such a line of attack was merited, albeit that I do not myself see the basis for such a conclusion. It follows that while Teva's attack on the credibility and independence of the expert witnesses called by BMS in these proceedings was a line of attack that may have caused a degree of personal affront, especially to Mr Chandler and Dr Young, I cannot conclude that it was a line of attack that ought not to have been made; sometimes counsel have to put unpleasant propositions to witnesses, albeit that they may gild those propositions with politeness.

1200. I turn now to consider in more detail why Teva's attack on the credibility and independence of the expert witnesses called by BMS in these proceedings has failed.

b. Mr Chandler

1201. Mr Chandler was a notably distinguished witness. He has served as a former Chancellor of the Delaware Court of Chancery and has enjoyed a successful career in private practice as an attorney. He clearly knew his law and, when questioned on the point, clearly knew the duties of an independent expert witness. There was no basis for impugning his independence or credibility. In this regard, the following might usefully be noted: (i) Mr Steele (a former Chief Justice of Delaware) is on the record (*e.g.,* in his evidence in the parallel proceedings in Finland and Sweden) as acknowledging the standing and reputation of Mr Chandler; (ii) Mr Chandler manifestly displayed his knowledge of the expectations and conduct of an independent expert witness when he was recalled to give evidence on 26th July 2023; (iii) at no stage in his cross-examination was Mr Chandler challenged to justify a disagreement with Mr Steele.

c. Professor Chisum

1202. Professor Chisum is a person of the highest repute. At no stage did Prof. Thomas, the expert witness called by Teva in Professor Chisum's area of expertise suggest otherwise. On the contrary, what comments he did make as to Prof. Chisum's standing was to acknowledge his standing and repute.

1203. It may be useful at this juncture to note Teva's proposition in its closing oral submissions (as I understood them) that when it comes to the briefing of expert witnesses it was unobjectionable for Teva to look at reports delivered elsewhere and provide them to their experts and ask their experts to comment

on them, but that when it came to Prof. Chisum, the gentleman engaged to deal with Prof. Thomas's evidence, there was an impropriety or a failure to brief him properly because he was presented with a report, instead of BMS engaging in an iterative process whereby he would be asked a series of questions, his analysis of those questions undertaken, and then he would be presented with the report. (The point, as I understand matters, also applied to most or all of BMS's witnesses.) Respectfully, I do not see such an iterative exercise to be required by law and consequently I do not see that BMS by failing to engage in such an iterative exercise was guilty of some impropriety in the manner in which it instructed or treated with Prof. Chisum (and neither do I see any impropriety to arise in terms of its dealings with its other expert witnesses in this regard). But even if counsel for Teva was right in this – and I do not see that he was – then, to use a colloquialism, 'what is sauce for the goose is sauce for the gander', *i.e.* the same standard would fall to be applied equally to both BMS and Teva. Yet Teva has consistently failed to meet the very standard that it would have me criticise BMS for not meeting. Thus, in:

– Dr Edwards's second statement (at §§1.2-1.3), he states:

> "*I have been provided with Dr Young's report, along with the documents he provided and those with which he had been provided. I have been asked to respond to Dr Young's report.*"

– Dr Gallagher's second statement (at §1.2) he states :

> "*I have been provided with Professor Morrissey's report, along with the documents he provided and those with which he had been provided. I have also been provided with the expert reports of Dr. Young and Dr. Taft.*"

– Dr Kinkeldey's second statement (at §3) she states:

> "*I make this replying expert witness statement in response to that of Mr. Christopher Rennie-Smith.*"

– Mr. Steele's statement (at §21), he states:

> "*I have reviewed the Holland report and have been asked to provide my observations and comments on two general topics addressed in that report.*"

– Prof. Thomas's statement (at §40), he states:

> "*I have had the opportunity to review the Holland Report which I understand was relied upon by BMS Ireland in the Italian proceedings. While I have the greatest respect for the late Justice Holland, I strenuously disagree with his conclusion...*".

(Because of the late Mr Holland's death there was no Holland report delivered in these proceedings, but the point is that a report on federal law was provided, after the Holland report had been furnished to Prof. Thomas and his opinion on same sought.)

– Prof. Thomas's second statement (at §2) he states:

> "*I have been provided with, and had the opportunity to review, the Statement of Professor Donald Chisum dated 13 May 2022 (the 'Chisum Statement'). My review of the Chisum Statement confirms my earlier opinion...*".

1204. I make no criticism of Teva or its lawyers or its expert witnesses for any failure to meet a standard that, however eloquently it was canvassed for by Teva, I do not see to be required by law. But neither does any such criticism fall to be levelled at BMS or its lawyers or its expert witnesses. And even if the standard canvassed for by Teva was required by law (and it is not), both parties would fall to be censured equally if such a standard fell to be applied. But the truth of matters is as was succinctly put by one of the counsel for BMS in their closing oral submissions:

> "*It was said yesterday that there was something extraordinary and 'disturbing' - Day 15, page 12 - that BMS's experts had been instructed to "respond to the experts from Teva". There is nothing unusual about this at all. That is the very function of a reply report. It is what experts are always asked to do in a replying report and it is what they always do. And it is indeed. Unsurprisingly. What Teva's experts were asked to do in their reply reports and what they did. The contrary proposition is again one that is, in my respectful submission, unarguable.*"

1205. Almost anything is arguable but here the argument made by Teva in this regard fails for the reasons that I have stated.

d. Mr Clarke

1206. As explained in my consideration of the evidence of Mr Granwell, Mr Clarke was expected to be called as an expert witness by BMS to deal with much the same area of evidence covered by Mr Granwell (who was called by Teva). Belatedly, on the cusp of being called to the witness box, Mr Clarke realised that he could not offer himself as an independent expert because he and/or his law firm do work for BMS. Perhaps Mr Clarke should have realised sooner than he did that he could not hold himself out as an independent expert witness; in truth he probably should have. But it appears that he did not realise that he was compromised until a late stage; once he did he told the BMS legal team; and counsel for BMS, once apprised of matters, rightly took the decision that, given that Mr Clarke could not hold himself out as an independent expert witness, he could not be called as an independent expert witness.

1207. I note in passing that the Supreme Court have confirmed that there is no clear judicial authority to support the drawing of an adverse inference from the withdrawal of an expert witness: *Doyle* v. *Banville* [2012] IESC 25, [2018] 1 IR 505 . That was a personal injuries case arising from a terrible motor accident which left Mr Doyle suffering from paraplegia. One of the grounds of appeal before the Supreme Court was that the trial judge had erred in law in failing to draw an inference from the failure of the defendant/respondent to adduce expert evidence. In the course of his judgment in the case, Clarke J., as he then was, observed as follows, at §3.5:

> "*While there may be cases where an inference can be drawn from a failure to call evidence of fact...it is not clear that an equivalent inference can properly be drawn from a failure to call expert evidence.*"

1208. Even if one could draw such an equivalent inference (and Clarke J. makes perfectly clear that it is not clear that one can) I do not see how such an equivalent inference could fall to be drawn on the just-described facts. That said, it may be (I do not know, and I am not about to pre-judge matters) that the belated withdrawal of Mr Clarke will fall to be re-visited at any costs hearings that follow on this judgment.

e. Mr Rennie-Smith

1209. Mr Rennie-Smith is a person of the highest repute. At no stage did Dr Kinkeldey, the expert witness called by Teva in Mr Rennie-Smith's area of expertise suggest otherwise. On the contrary, what comments she did make as to Mr Rennie-Smith's standing was to acknowledge his standing and repute.

f. Professor Taft

1210. Professor Taft is a distinguished individual of the highest repute. However, for the particular purposes of the present proceedings, his evidence presents with the difficulties that I have identified previously above.

g. Dr Young

I. Some Criticisms Made By Teva

1211. It was striking to me as I listened to the cross-examination of Dr Young just how much time was spent on attacking the credibility of his evidence on the basis that (i) he was looking at matters with hindsight, or (ii) was guided by the lawyers as to what he should say with the result that he lost his independence.

II. Guided By the Lawyers?

1212. As to (ii), it seemed to me that Teva's criticisms in this regard made no allowance for the "*rather unusual position*" of expert witnesses in patent litigation, as recognised by Arnold J. in *Medimmune v Novartis* [2011] EWHC 1669 (Pat.), as considered above. Turning to the detail of the allegations put to Dr Young:

- Dr Young explained that he had discussions with WilmerHale when first instructed and he explained the process that was followed. He made clear that he wrote the description of the state of play himself from the materials and his own knowledge. The papers referred to are set out and it does not appear that there is any suggestion that there is anything wrong with this part of his evidence, as none of it was challenged.
- Dr Young was given the prior art and the 652 application in sequence. He was asked whether he could derive the structures of the molecules in embodiment 8 and demonstrated to Wilmerhale that he could. Only once he had done this was he given the set of drawn-out structures from the worked examples of 652 to make his task easier. None of this was directly challenged in cross-examination. To the extent that it was suggested (and it did seem at least implicitly to be suggested) that he was directed in this regard there is no evidence to support this.
- There was some suggestion that slight differences of language in the way that Dr Young introduces the three analyses was suggestive that some of the analyses were done for him seems, with all respect, absurd: such differences in wording happen. In any event, Dr Young made clear that there was no substance to the suggestion.
- Dr Young made clear that he was told to put his knowledge of apixaban out of his mind when preparing his evidence. It is right and proper that he was told this, and there is no evidence to suggest that he did anything other than what he was told to do in this regard.

1213. Some coincidences between the evidence of Dr Camp (a medicinal chemist who gave evidence in London) and Dr Young were put to Dr Young in cross-examination, again I believe to suggest that Dr Young was directed by BMS as to what he should say in these proceedings.

1214. Before proceeding I should perhaps note that there are at least two meanings to the word 'coincidence'. Thus, it can mean (1) that there is a correspondence in nature or time of a particular occurrence (*e.g.*, two people being born in the same hospital on the same day), and (2) a remarkable concurrence of events or circumstances without apparent causal connection. These are innocent coincidences and I believe I can take judicial notice that innocent coincidences happen in life. What Teva seemed to suggest was something more sinister, *i.e.* that such coincidences as it identified flowed (perhaps even necessarily flowed) from some impropriety. I consider the coincidences that Teva

highlighted hereafter. There is no evidence before me of any improper/sinister dimension to these coincidences, I have the evidence of Dr Young explaining the propriety of his actions in these proceedings, and I accept that he acted with propriety; all I see in each of the coincidences raised is some level of explainable (and explained) innocent coincidence.

Coincidence #1*: Both Dr Camp and Dr Young identify a similar set of papers as containing relevant material for the purposes of determining the state of play in the field.*

Dr Young indicated in his evidence that he was given a bundle of papers, asked whether they represented the state of art at the priority date, and concluded that they did. He was clear in his evidence that he was not told that they were key documents. He brought his own involvement in the field at the priority date to bear. And he also indicated that he had done some of his own searches in any event to determine that the papers were representative. I must admit that when this coincidence was under consideration, the first thought that occurred to me was whether this was a case of two medicinal chemists being asked to identify the material that they considered to reflect the state of the art at the priority date and alighting, unsurprisingly, on the same papers, all of which are reviews of the work being done at the time or papers from those who had identified interesting molecules. In fact, Dr Young made this very point himself and I find it a convincing one. I should perhaps also note that in their closing written submissions, counsel for BMS also make the following persuasive point:

> "*In considering the merit of the attack, it is perhaps worth pointing out that Dr Redshaw, the medicinal chemist who gave evidence for Teva in the UK also identified pretty well the same range of material. We attach an extract from her report listing the reports that she found in her search which shows that it …overlaps very closely with the materials identified by Dr Young and Dr Camp. If we look at the list of papers produced by Dr Redshaw, it includes eight of the ten papers listed by Dr Young in paragraph 5 of his second statement. It can hardly be suggested that there was collusion between Dr Redshaw and Dr Young.*"

One really had only to listen for a short time to Dr Young in the witness box to know that he is a transparently truthful gentleman. He was also clear in his evidence, honestly given, that he would not offer as his opinion an opinion that he had not independently formed, and he would not have been willing to say whatever he was told. I fully accept Dr Young's good faith and honesty in this regard.

For the reasons just given I conclude that there is nothing sinister or improper about the above coincidence.

Coincidence #2*: The conclusions that Dr Camp and Dr Young reached, on analysing the material in the CGK and the specification, that apixaban was likely to be an effective factor Xa inhibitor were similar.*

Three points might be made: (i) the technical conclusions were similar (as one instinctively would expect if both men were correct in their reasoning); however, the wording used in their reasoning was not similar; (ii) as I have just touched upon, if one asks two similarly qualified medicinal chemists to review the same technical material and express their reasons for thinking that Example 18 is a plausible factor Xa inhibitor, it seems likely that they will arrive at the same technical conclusions; one really had only to listen for a short time to Dr Young in the witness box to know that he is a transparently truthful gentleman. He was also clear in his evidence, honestly given, that he would not offer as his opinion an opinion that he had not independently formed, and he would not have been willing simply to say whatever he was told. I fully accept Dr Young's good faith and honesty in this regard.

For the reasons just given, I conclude that there is nothing sinister or improper about the above coincidence.

Coincidence #3: *There is a similarity in the molecules selected by Dr Camp and Dr Young.*

Three points might be made in this regard. First, there is not much of a coincidence: the molecules that the two men identified are not in fact the same. Second, the same (or closely related) molecules to those identified by Dr Young are identified in the agreed CGK document (a document agreed by experts on both sides, and I doubt there was mass collusion). Third, Dr Young was not even particularly settled on the molecules he identified: his evidence was that he chose them as illustrative examples (and could have chosen others from the same series).

For the reasons just given, I conclude that there is nothing sinister or improper about the above coincidence.

1215. Lest the point be lost, I see nothing to the above coincidences but expectable, explainable and explained happenstance.

III. Hindsight?

1216. I turn now to the proposition that Dr Young looked at matters with hindsight, using his knowledge of apixaban to guide his analysis of the 652 application and the pre-priority date papers. Dr Young, a transparently honest witness, made it clear that he put this knowledge aside and worked on the basis only of the information in the CGK and the 652 specification. That said it does seem to me that there was possibly a degree of hindsight in the focus on embodiment 8 and the worked examples.

IV. The First Person Plural

1217. Teva complains that Dr Young referred to "*our case*". Dr Young was in the witness box on Days 13 and 14. A search of the transcript for both days yields a nil return for the phrase "*our case*". Nor do I find that phrase in his written statements.

1218. Teva complains in its written submissions that Dr Young used the first person plural instead of the first person singular when referring to the preparation of his report. I have already dealt with how the report was prepared. I do not see any significance to his use of the first person plural. At no point did I consider that Dr Young was somehow identifying himself or his interests with BMS or somehow acting as a less than independent expert witness. As mentioned above, one really had only to listen for a short time to Dr Young in the witness box to know that he is a transparently truthful gentleman. He was also clear in his evidence, honestly given, that he would not offer as his opinion an opinion that he had not independently formed, and he would not have been willing simply to say whatever he was told. I fully accept Dr Young's good faith and honesty.

h. When Things Go Wrong

1219. As for the exclusion of evidence in the event of a breach, I should perhaps just mention the decision in *Kenneally* v. *De Puy International Ltd* [2016] IEHC 728, [2017] 2 IR 487 to show how slow the courts are to exclude evidence, even when some breach presents. By way of background to that case it is, I understand, possible to bring a form of action in the United States that is known as a *qui tam* action. ('*Qui tam*' is a shorthand reference to the Latin phrase '*qui tam pro domino rege quam pro se ipso in hac parte sequitur*', *i.e.* 'Who sues on behalf of the king as well as for himself'). In a *qui tam* action a relator brings an action against a person or company on behalf of the government. In his judgment in *Kenneally*, Barton J. describes this form of action and the issue presenting in the personal injuries action before him:

"*19.* *The Court has been given to understand that the American proceedings are a form of public interest litigation made possible by virtue of both Federal and State legislation dating back to 1863 during the American Civil War the purpose of which is, in essence, to encourage citizens...to initiate proceedings which expose fraudulent activities of a commercial nature which have resulted in loss to the Government or the States or their agencies.*

20. *Whereas this litigation is usually commenced by private litigators, the Federal Government or State or State agency may seek to join in the proceedings at any stage....*

21. *Success in the proceedings for the Government or State creates an entitlement to damages in respect of any losses arising from the activities with which the proceedings are concerned, such as from the manufacture and supply of defective goods; success also has a benefit for the initiating litigators...since they are entitled to a percentage or proportion of the damages recovered.*

...

23. *It is the very significant financial interest which may flow from the 'qui tam' litigation which the Defendant submits robs Mr. Langton of any independence or objectivity as an expert in these proceedings. Critically, the Defendant contends that there is a clear nexus between that litigation and this suit. Accordingly, it was argued that Mr. Langton has no option but to give the same evidence in both cases whereas a truly independent and objective expert should be free, on due consideration, to accept the evidence or opinion, when put, of an expert intended to be called by an opposing party.*

24. *Having nailed his colours to the mast in the* qui tam *litigation, the Defendant contends that Mr Langton has deprived himself of the freedom to agree with an expert view contrary to his own, moreover, because the outcome of these proceedings may directly impact upon the qui tam litigation with the potential for significant financial reward should that be successful, he has to give evidence in these proceedings consistent with the cause he advocates in the 'qui tam' litigation.*"

1220. Even in these circumstances Barton J. ultimately determined that he would not exclude the expert evidence of Mr Langton. So even if there was a breach of the applicable law or rules in the manner in which BMS has instructed its expert witnesses (and I do not see that there is) the decision in *Kenneally* points to just how slow the courts are to exclude evidence even when a breach presents. Given that Teva has in any event succeeded on the plausibility/validity limb of these proceedings, I do not see that there is need to consider the implications (if any) of the possible hindsight, doubtless unintended, in Dr Young's focus on embodiment 8 and the worked examples.

XIII. CONSOLIDATED CASES G0001/22 AND G0002/22

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Consolidated Cases G1/22 and G2/22

A. Introduction

1221. Some weeks after I reserved judgment in this case, the EPO's Enlarged Board of Appeal handed down its decision in Consolidated Cases G0001/22 and G0002/22 (Consolidated Appeals T1513/17-3.3.04 and T-2719/19-3.3.04). The parties brought my attention to this judgment, made further written submissions concerning the decision, and clearly wished for me to include a consideration of same in my judgment.

1222. In the headnote to the decision of the Enlarged Board, the key findings of that decision are summarised as follows:

> "I. *The European Patent Office is competent to assess whether a party is entitled to claim priority under Article 87(1) EPC.*[8]
>
> *There is a rebuttable presumption under the autonomous law of the EPC that the applicant claiming priority in accordance with Article 88(1) EPC*[9] *and the corresponding Implementing Regulations is entitled to claim priority.*
>
> *II. The rebuttable presumption also applies in situations where the European patent application derives from a PCT application and/or where the priority applicant(s) are not identical with the subsequent applicant(s).*
>
> *In a situation where a PCT application is jointly filed by parties A and B, (i) designating party A for one or more designated States and party B for one or more other designated States, and (ii) claiming priority from an earlier patent application designating party A as the applicant, the joint filing implies an agreement between parties A and B allowing party B to rely on the priority, unless there are substantial factual indications to the contrary.*"

1223. I consider hereafter the substance of the decision of the Enlarged Board, the supplemental submissions that have been made to me by the parties, and the implications that I see the decision of the Enlarged Board to have for the case now before me. Because the decision issued when my judgment was almost finished, my consideration of Cases G1/22 and G2/22 appears in this separate, later chapter of my judgment.

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[8] Article 87(1)/EPC provides, amongst other matters, as follows:

> "*Any person who has duly filed, in or for (a) any State party to the Paris Convention for the Protection of Industrial Property or (b) any Member of the World Trade Organization, an application for a patent...or his successor in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application.*"

[9] Article 88(1)/EPC provides as follows:

> "*An applicant desiring to take advantage of the priority of a previous application shall file a declaration of priority and any other document required, in accordance with the Implementing Regulations.*"

B. The Decision of the Enlarged Board of Appeal

1. The Referred Questions

2.

1224. By interlocutory referring decision dated 28th January 2022, in consolidated proceedings T-1513/17 and T-2719/19 the EPO's Technical Board of Appeal referred the following questions of law to the Enlarged Board of Appeal:

> "*I.* *Does the EPC confer jurisdiction on the EPO to determine whether a party validly claims to be a successor in title as referred to in Art.87(1)(b) EPC?*[10]
>
> [The Enlarged Board rephrased this question as follows (at §34): "Is the EPO competent to assess whether a party is entitled to claim priority under Art.87(1) EPC?"]
>
> *II.* *If question I is answered to the affirmative*
>
> *Can a party B validly rely on the priority right claimed in a PCT-application for the purpose of claiming priority rights under Art.87(1) EPC in the case where:*
>
> *1)* *a PCT-application designates party A as applicant for the US only and party B as applicant for other designated States, including regional European patent protection, and*
> *2)* *the PCT-application claims priority from an earlier patent application that designates party A as the applicant, and*
> *3)* *the priority claimed in the PCT-application is in compliance with Article 4 of the Paris Convention?*"[11]
>
> [This question covered a particular situation occurring where a party, typically the inventor/s, filed a US priority application (also in the form of a provisional application) which was then used as priority application for a later PCT application, designating one party (typically still the inventor/s) for the US and another party (typically the employer of the inventor/s) for European patent protection. Before the America Invents Act (2011) entered into force, only the inventor/s could be applicants in a US patent application. The priority application in the referral before the Enlarged Board of Appeal, had been filed in 2004, long before the coming into being of the said Act and thus had to be filed by the inventors under the then applicable laws.]

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[10] Article 87(1)(b)/EPC provides, amongst other matters, as follows:

> "*Any person who has duly filed, in or for...(b) any Member of the World Trade Organization, an application for a patent...or his successor in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application.*"

[11] Article 4A(1) of the Paris Convention provides, amongst other matters that:

> "*Any person who has duly filed an application for a patent...in one of the countries of the Union, or his successor in title, shall enjoy, for the purpose of filing in the other countries, a right of priority during the periods hereinafter fixed*."

Article 4(C)(1), amongst other matters, sets this priority period at 12 months for patents.

2. The Underlying Dispute in T-1513/17

1225. European patent application No. 05 779 924.9, published as international application WO 2005/110481 with the filing date of 16th May 2005, claimed priority of US provisional patent application No. 60/571,444, filed on 14th May 2004 (the priority application). The priority application was filed in the name of R.P. Rother, H. Wang and Z. Zhong, the inventors. The PCT application named the three inventors as inventors and as applicants for the USA only. For all designated states except the USA, it named Alexion Pharmaceuticals, Inc. and the University of Western Ontario as applicants.

1226. European patent No. 1 755 674 (the patent in suit) was granted on the basis of application 05 779 924.9 on 19th November 2014. Since the University of Western Ontario had assigned its right to the patent application to Alexion Pharmaceuticals in 2007, the patent in suit named Alexion as the sole patent proprietor and named R.P. Rother, H. Wang and Z. Zhong as inventors. The patent in suit was revoked after opposition proceedings instituted by Novartis AG, F. Hoffmann-La Roche AG, and Chugai Pharmaceutical Co. Ltd.. The grounds of opposition included lack of novelty over certain documents published after the filing date of the priority application but prior to the filing date of the patent in suit. The validity of the priority claim was contested, amongst other matters, because the applicants, Alexion and the University of Western Ontario, were alleged not to be the applicants or the successors in title of the applicants of the priority application. The priority right was found invalid because only the priority right of one of the three inventors had been assigned to Alexion. An assignment of the other two inventors to Alexion or to the University of Western Ontario had not taken place prior to the filing of the PCT application. As a consequence of the invalid priority right, the opposition division found, amongst other matters, that claim 1 of the main request lacked novelty.

3. The Underlying Dispute in T-2719/19

1227. European patent application No. 16 160 321.2 was filed as a divisional application of an earlier divisional application derived from application EP 05 779 924.9. Based on the same PCT application as the patent in suit, the application in suit also claimed priority from US provisional application No. 60/571,444, referred to above. During the examination proceedings, the same issues concerning the priority claim were invoked as outlined above. The same documents as were used in the opposition proceedings concerning the patent in suit were invoked against the subject-matter of the application in suit. And for the same reasons as outlined above, the priority was found invalid. Consequently, the application in suit was refused because certain intermediate publications were found to be novelty-destroying prior art. Appeal proceedings followed on and the above-quoted questions were eventually referred to the Enlarged Board of Appeal.

4. The EPC Provisions on Priority

1228. In its decision, the Enlarged Board of Appeal provides a summary of the EPC decisions on priority which may be summarised as follows:

[1] Articles 87-89 EPC provide a complete, self-contained code of rules on the subject of claiming priority for the purpose of filing a European patent application. (§25).

[2] Since the EPC constitutes, according to its preamble, a special agreement within the meaning of Art.19 of the Paris Convention, the EPC provisions on priority are intended not to contravene the basic principles concerning priority of that convention. (§25).

[3] Article 87/EPC and Art.88(2)-(4)/EPC are concerned with the material conditions under which priority rights may be derived from an earlier application. (Article 88(1)/EPC concerns the procedural requirements to be

met by an applicant desiring to take advantage of the priority of an earlier application. These procedural requirements are supplemented by the Implementing Regulations (Rules 52 to 54 EPC)). (§26).

[4] Article 89 EPC prescribes the effect of a priority right, *i.e.* that the priority date counts as the date of filing of the European patent application for the purposes of the delimitation of the prior art under Arts.54(2) and (3) EPC.[12] (§26).

[5] As regards the Article 87(1)/EPC "*same invention*" criterion, this is regularly an issue in examination and opposition proceedings. (The referral before the Enlarged Board in the present case concerned the question whether the applicant of the later application is entitled to claim the priority of the earlier application, in particular as a successor of the applicant of the priority application). (§28).

[6] With respect to the definition of the parties entitled to claim priority from an earlier patent application, the provisions of Article 4A(1) Paris Convention and of Article 87(1) EPC are identical. (§30).

5. Admissibility.

1229. The Enlarged Board considered the admissibility of the referral and decided that both questions posed to it were admissible. (§§43 *et seq.*)

6. The "Right of Priority" and its Assignment under Art.87 EPC

1230. Under the above heading the Enlarged Board made the following observations:

I. Purpose of Priority Rights

[1] The basic purpose of the right of priority is to safeguard, for a limited period, the interests of patent applicants in their endeavour to obtain international protection for their inventions, thereby alleviating the negative consequences of the principle of territoriality in patent law. (§54).

[2] The priority provisions contained in the Paris Convention should not be regarded as a body of exception clauses which should be interpreted strictly. (§54).

[3] On the contrary, the Rules of the Paris Convention and the self-contained priority system of the EPC should be construed in a manner which ensures that the above-mentioned general purpose is fulfilled as far as possible. (§54).

[4] For the person filing a patent application in a state addressed in Art.87(1) EPC, the priority system means that it has the option to file a bundle of subsequent applications for the same invention in a freely selected group of other territories where each of the later (national or regional) applications may benefit from the priority date of the first application. (§55).

[5] The priority period of twelve months on the one hand allows for an evaluation by the applicant as to where patent protection should be sought. On the other hand, the clear limitation of the period provides legal certainty to third parties who ought to know the geographical limitations of the patent protection they may be confronted with. (§55).

[6] The effect of the priority right (namely, the exclusion of intermediate prior art) often concerns publications originating (ironically) from the priority applicant or persons connected with it. (§56).

[12] In other words, the priority right allows the exclusion of everything that has become prior art between the priority date and the filing date (the so-called 'intermediate prior art') for the assessment of patentability.

[7] The priority right thus also protects an applicant from its own intermediate prior art and allows it to publish the content of the priority application before the subsequent applications are filed. (§56).

[8] This last aspect is of particular relevance in a patent system like the European patent system that generally does not provide grace periods prior to filing a patent application during which publications of the applicant are non-prejudicial. (§56).

[9] Only the subsequent application (for which priority is claimed) and the respective applicant may benefit from the priority right. For the priority application, the priority right derived therefrom is irrelevant since for the priority application there is no period between the priority date and the application date (and, consequently, no intermediate prior art). (§57).

II. Priority Entitlement Challenges

[10] Following a brief consideration of EPO case-law (at §§58-60), the Enlarged Board of Appeal concluded that despite the relative rarity of priority entitlement challenges during the early decades of the EPO, its case-law has been substantially uniform in the last 10-15 years, with the EPO being viewed to have the jurisdiction to decide who is entitled to claim priority. (§61). Less settled is *how* the EPO should decide disputes on entitlement to priority. (§61).

III. National Law and the Assessment of Succession

[11] National law is applicable to the succession in title addressed in Art. 87(1)/EPC. (§62).

[12] The EPC contains no conflict of laws rules for the determination of the applicable national laws, except for Art.60(1) EPC.[13] (§62).

[13] The EPC does not contain, in particular, any conflict of laws rules applicable to the transfer of rights from an applicant other than the inventor/s to the successor/s of such applicant. (§62).

[14] Conflict of laws rules concerning the succession under Art.87(1) EPC could refer to a range of different national laws, e.g., the law of the country where the first application was filed (lex originis), the law of the country where the subsequent application was filed (lex loci protectionis), the law of the country which is agreed upon in the relevant contract (lex loci contractus), and the law of the country where at least one of the parties to the transfer has

[13] Article 60(1)/EPC provides as follows:

> "*The right to a European patent shall belong to the inventor or his successor in title. If the inventor is an employee, the right to a European patent shall be determined in accordance with the law of the State in which the employee is mainly employed; if the State in which the employee is mainly employed cannot be determined, the law to be applied shall be that of the State in which the employer has the place of business to which the employee is attached*."

As the Enlarged Board explains in its decision (at §62), the rule in Art.60(1) is addressed to the national courts of the contracting states when assessing disputes concerning the right to a European patent as addressed in Article 61(1) EPC, which last provision provides as follows:

> "*If by a final decision it is adjudged that a person other than the applicant is entitled to the grant of the European patent, that person may, in accordance with the Implementing Regulations:* ***(a)*** *prosecute the European patent application as his own application in place of the applicant;* ***(b)*** *file a new European patent application in respect of the same invention; or* ***(c)*** *request that the European patent application be refused.* "

its residence (lex domicilii). (§63). Any one of these options may yield further uncertainties. "*In sum, the private international law aspects of Article 87(1) EPC can be described as complex*" (§64).

[15] So far, no clear preference has been expressed for any choice of law rule in the EPO case law. (§65). In cases where the applicable national law is determined, national provisions are regularly applied by the boards of appeal. (§66).

IV. Autonomous Substantive Law under the EPC

[16] Under Art.87(1)/EPC transfer of the right of priority has to have been concluded before the filing of the subsequent European patent application. (§68).

[17] Unsettled as yet is whether an equally high standard of proof for the transfer of priority rights as the one required for the assignment of a European patent application, with decisions as yet going both ways on this point. (§69).

V. National Case-Law Under Art.87/EPC

[18] If questions of entitlement to claim priority under Art.87(1) EPC arise in national proceedings, the court seised needs to address all issues concerning the applicant's identity or succession, including the determination and application of foreign laws. (§70).

[Court Note: I note that where, as is the case in the present proceedings, questions of entitlement to claim priority under Art.87(1) EPC arise in national proceedings, the court seised needs to address all issues concerning the applicant's identity or succession, including the determination and application of foreign laws. I note at this juncture but it is true generally of the decision of the Enlarged Board, that the Board consistently acknowledges the fact that national courts have and can apply national conflict of law rules; there is no suggestion that only the 'new EPC law' falls to be applied.]

[19] In proceedings before national courts, conflict of laws issues and the related application of foreign law tend to cause less concern than in proceedings before the EPO. (This is because (i) national courts can rely on their applicable conflict of laws rules and case law, (ii) the domestic (substantive) laws of the national court are often applicable, either because (a) the applicable conflict of laws rules refer to it or (b) conflict of laws issues are not relevant in cases not having connections to more than one jurisdiction. (§70).

[20] If the facts of a case involve one or more jurisdictions other than the court's own jurisdiction, the court's set of conflict of laws rules is applied by first qualifying the legal relationship at issue in view of the individual conflict of laws rule that may be applicable. (§71).

VI. Transfer of different rights to the subsequent applicant claiming priority

At para. 74 the EPO moves on to consider how an inventor (or her employer or other legal successor) may obtain international patent protection, using the priority system established under the Paris Convention. Thus, it notes how:

[1] an inventor may apply for a patent in every territory or may transfer the right to obtain a patent to separate applicants for the different territories. (§75).

[2] inventors often assign the right to the patents in all territories to a single applicant who then files a priority application. (§75).

[3] within the priority period, the priority applicant or other applicants may file patent applications in other territories which benefit from the application date of the priority application (i.e. the priority date). (§75).

[4] within international groups of companies, the inventor's employer company may acquire the rights for all territories and then vest its subsidiaries in the different territories with the patent rights for the respective territories. (§76).

[5] the possibilities mentioned in [4] reflect the fact that the title to a patent application is a property right that is established and may be transferred for each territory in accordance with the laws of the respective territory. (§76).

[6] the priority right may be obtained only as a consequence of the filing of the priority application. (§77).

[7] the priority applicant needs to provide any subsequent applicant with the documents required in the respective territory for claiming priority. (§77).

[8] the priority right remains relevant for the subsequent application and any patent based thereon but is not relevant for the priority application. (§77).

[9] if the priority applicant (Applicant A) transfers the title to the subsequent application to the subsequent applicant (Applicant B), this transfer is normally realised together with the transfer of the priority right. (§78).

[10] in agreements discussed in previous EPO priority entitlement cases, no distinction has usually been made between the two transfers. (§78).

[11] in existing EPO case law under Art.87(1) EPC, it is not always clear whether the transfer at issue encompasses only the priority right or also the title to the subsequent European application. However, the fact that different parties are potentially involved in the transfer of the different rights already shows that a clear distinction should be made between the title to the subsequent application and the priority right, i.e. the right to attribute the date of the priority application to this application. (§78).

[12] only the transfer of the priority right is relevant for the proceedings before the EPO for the purposes of Article 87(1) EPC. (§78).

7. Competence and applicable law for the transfer of the different rights invoked by the subsequent applicant

1231. Under the above heading the Enlarged Board made the following observations:

I. Title to the subsequent application

[1] In proceedings before the EPO, the applicant is deemed to be entitled to exercise the right to the European patent (Art.60(3) EPC).[14] (§79).

[2] The EPO has no power to decide a dispute as to whether a particular applicant is legally entitled to apply for and be granted a European patent in respect of the subject-matter of a particular application. (§79).

[3] The determination of questions of entitlement to the right to the grant of a European patent prior to grant is governed by the Protocol on Jurisdiction and the Recognition of Decisions in respect of the Right to the grant of a European patent, which is an integral part of the EPC. (§79).

[4] The Protocol on Recognition governs the jurisdiction of the national courts of the contracting states for disputes on entitlement to European patent applications. (§79).

[14] Article 60(3)/EPC states simply that "*In proceedings before the European Patent Office, the applicant shall be deemed to be entitled to exercise the right to a European patent.* "

[5] After grant, the national courts are competent to decide on disputes on the title to the European patent for each of the designated contracting states. (§79).

[6] During disputes on the right to the grant of a European patent, the proceedings for grant before the EPO are regularly stayed in accordance with the provisions of Rule 14 of the Implementing Regulations.[15] (§79).

[7] Disputes on the title to a European patent application or patent are resolved by the national courts by first determining the applicable law, applying their conflict of laws rules. (§80).

[Court Note: As can be seen the Enlarged Board's decision confirms that disputes on the title to a European patent application or patent are resolved by the national courts by first determining the applicable law, applying their conflict of laws rules.]

[8] Article 60(3)/EPC applies to the applicant of any European patent application, regardless of whether it is a priority or first application or a subsequent application. (§81).

[9] As far as title to the priority application is concerned, Article 60(3)/EPC is not directly applicable, unless the priority application is a European application. (§82).

[10] If the title to the subsequent European patent application has been acquired from the priority applicant, national courts may have to assess under the applicable national laws who was entitled to the priority application in order to establish the chain of transfers leading to the subsequent applicant. (§82).

[Court Note: I note at this juncture, though it is true generally of the decision of the Enlarged Board, that the Board consistently acknowledges the fact that national courts may need to apply national law in circumstances such as the priority issue now presenting before me. It seems to me that in §82 the Enlarged Board contemplates that I would engage in precisely the type of exercise that I have undertaken in this judgment, assessing by reference to the law of Delaware how the priority issue falls to be resolved.]

II. Right to claim the priority date for the subsequent application

[11] The right to priority (*i.e.* the right to claim priority for a European patent application from the filing date of an eligible 'first application' or 'previous application' originates in the applicant of the first application). (§83).

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[15] Under Rule 14(1):

> "*If a third party provides evidence that he has instituted proceedings against the applicant seeking a decision within the meaning of Article 61, paragraph 1, the proceedings for grant shall be stayed unless the third party communicates to the European Patent Office in writing his consent to the continuation of such proceedings.* "

Under Art.61(1)/EPC:

> "*If by a final decision it is adjudged that a person other than the applicant is entitled to the grant of the European patent, that person may, in accordance with the Implementing Regulations: (a) prosecute the European patent application as his own application in place of the applicant; (b) file a new European patent application in respect of the same invention; or (c) request that the European patent application be refused.*"

[12] The prevailing literature also assumes that the first application, not only a subsequent application, establishes the priority right under the Paris Convention. (§83).

[13] The filing of a first application may be seen as the creation of a bundle of potential priority rights that come into existence and may be examined only when they are invoked in a subsequent application. (§83).

[14] For the subsequent application, priority rights are governed exclusively by Articles 87 to 89 EPC. (§84).

[15] While it is open to discussion whether the priority right with the priority applicant is established under Art.87(1)/EPC or under the Paris Convention, certainly no national laws are involved when a priority right is created or claimed for a subsequent application. This is a significant difference to the title to a European patent application or patent, which depends upon national laws (e.g., employment law or property law). (§84).

[16] Since the creation, the existence and the effects of the priority right are governed only by the EPC (and by the Paris Convention through its relationship with the EPC), priority rights are autonomous rights under the EPC and should be assessed only in the context of the EPC, regardless of any national laws. (§85).

[17] Consequently, the entitlement to claim priority (and any related assignments of priority rights) should also be assessed under the autonomous law of the EPC. (§86).

[18] The autonomous requirements for the valid transfer of priority rights should not be stricter than national rules applicable to the transfer of priority rights or other property rights. (§86).

[19] The referring board noted, the EPC does not impose any formal requirements for the transfer of the priority right by agreement. (§86).

[20] From the perspective of the EPC, the legislation of the EPC and related international treaties, such as the Paris Convention and the PCT, is autonomous. (§87).

[21] While it has often been discussed whether Art.60(3) EPC could be applied by analogy to the right of priority addressed in Art.87(1) EPC, this argument ceases to be pertinent if entitlement to priority is assessed exclusively under the autonomous law of the EPC. (§88).

[22] The Enlarged Board considers that the EPC drafters intentionally left open the question of the EPO's competence to decide on the priority entitlement. Consequently, there is no lacuna in this respect that could be filled by an application by analogy of Art.60(3) EPC. (§89).

[23] As regards the separation of powers between national courts and the EPO enshrined in Art.60(3) EPC, such separation of powers can be respected even when the EPO is competent to assess priority entitlement if a clear distinction is made between, on the one hand, *the priority right and its transfer* as a matter governed by the autonomous law of the EPC and assessed by the EPO, and, on the other hand, *the title to the subsequent application and its transfer*, which is governed by national laws and assessed by national courts. (§90).

[24] Acknowledging the EPO's competence to assess priority entitlement respects the argument that the EPO, in view of Art.87(1) EPC, has to assess all aspects of the right of priority and that no distinction should be made between the 'where', 'what' and 'when' requirements on the one hand and the 'who' requirement on the other. (§91).

[25] If all four requirements relevant under Art.87(1) EPC are assessed by the EPO, the EPO is competent for all aspects that may be relevant to determine the prior art, enabling it to assess all aspects of patentability. In contrast, national courts would remain competent to assess entitlement to the patent

application or patent without getting involved in any questions related to patentability. (§91).

[26] Even if the 'who' requirement underlying Art.87(1) EPC is related to entitlement issues, it is clearly a criterion relevant for the validity of the patent based on the subsequent application since it is relevant for the delimitation of the prior art. (§92).

[27] If the EPO can assess all aspects of the determination of prior art, the EPO's finding on patentability is based on a comprehensive assessment. (Conversely, if the EPO was barred from assessing priority entitlement, situations could arise in which the EPO has evidence potentially affecting the patentability of an invention but cannot use such evidence in its decision on patentability). (§92).

[28] Disputes on the entitlement to the patent, on the other hand, do not affect the EPO's findings on the patentability of the invention and the evidence and assessments underlying such findings, such as the EPO's determination of the relevant prior art. (§92).

8. National and Autonomous Considerations on Succession under Art. 87(1)/EPC

1232. Under the above heading the Enlarged Board made the following observations:

I. Priority entitlement and contractual succession assessed under national laws/by national courts

[1] Agreements under which the subsequent applicant acquires the title to the subsequent application and the right of priority usually fail to distinguish between the two rights. (§93).

[2] Across Europe there are differing views on the relevance of the right of priority addressed in Art.87(1) EPC as a property right separate from the title to the subsequent application for which the priority is claimed. There is a widespread view that the priority right is a mere ancillary right to the right to the subsequent patent application or patent which automatically follows any transfer of the title to the patent application or patent or, depending on the jurisdiction, that the title to the subsequent application automatically implies priority entitlement. (§97).

[3] These views do not consider the possibility that the title to the subsequent application has not been acquired from the priority applicant. They also do not sufficiently reflect the fact that the priority applicant does not just transfer a right but needs also to provide active support to the subsequent applicant wishing to benefit from this right. (§97).

[4] Such disregard for the priority right or its interpretation as a mere ancillary right to the right to the subsequent application may partly explain why the priority right is rarely addressed in agreements on the transfer of the patent right. (§98).

[5] The Enlarged Board is not aware of national statutes or case law setting higher formal requirements for the transfer of the priority right than for the transfer of the right to the patent application. (§98).

II. Consequences for the autonomous assessment of transfers of priority rights

[1] In most jurisdictions, rights to obtain a patent can be transferred without any written agreement or other formalities. (§99).

[2] The right to priority automatically follows the title to the subsequent patent application in many jurisdictions and may thus also be transferred informally. (§99).

[3] If national laws establish low or no formal requirements for the transfer of priority rights, the autonomous law of the EPC should not establish higher formal requirements than those established under national laws that may be relevant in the context of a European application. (§99).

[4] On the contrary, the EPO should adapt itself to the lowest standards established under national laws and accept informal or tacit transfers of priority rights under almost any circumstances. (§99).

[5] For example, the autonomous law of the EPC should not require that the assignment of priority rights has to be in writing and/or has to be signed by or on behalf of the parties to the transaction since this would establish a high threshold in view of the national laws. (§100).

[6] Even the requirement that the transfer of the right of priority needs to be concluded before the filing of the subsequent European patent application is questionable in the Enlarged Board's view. (§100).

[7] If there are jurisdictions that allow an ex post ('nunc pro tunc') transfer of priority rights, the EPO should not apply higher standards. (§100).

[8] The allowability of a retroactive transfer of priority rights may have limited practical relevance if priority entitlement is presumed to exist on the date on which priority is claimed for the subsequent European application. (§100).

III. Rebuttable presumption of entitlement to claim priority

[1] Low standards for a valid transfer of priority rights not only serve the purpose of harmonisation with national laws that could be applicable instead of the autonomous law of the EPC. They serve the purpose of priority rights, namely to facilitate international patent protection, by reducing the risk that the inventors' (or their legal successors') interest in obtaining patent protection in multiple jurisdictions is jeopardised by formal requirements they may inadvertently fail to meet. (§101).

[2] Any party transferring the right to a subsequent application wishes, under normal circumstances, that the subsequent applicant may benefit from the priority right. (Given that the title to the priority application and the title to the subsequent application originate from the same inventor who normally desires that the priority is valid for all subsequent applications, it must be assumed that the priority applicant who has not acquired the right to the subsequent application accepts or at least tolerates the use of the priority by the subsequent applicant). (§102).

[3] The formal requirements for claiming priority in accordance with Art.88(1)/EPC can only be met by the subsequent applicant if the priority applicant provides the necessary support completely and in time. The fulfilment of these requirements can thus be seen as strong factual evidence of the priority applicant's approval of the subsequent applicant's entitlement to priority. (§104).

[4] Entitlement to priority should in principle be presumed to exist to the benefit of the subsequent applicant of the European patent application if the applicant claims priority in accordance with Art.88(1) EPC and the corresponding Implementing Regulations.[16] (§105).

[16] This conclusion was reached by the Enlarged Board having taken into account (i) that the priority applicant or its legal predecessor must under normal circumstances be presumed to accept the subsequent applicant's reliance on the priority right, (ii) the lack of formal requirements for the transfer of priority rights and (iii) the necessary cooperation of the priority applicant with the subsequent applicant in order to allow the latter to rely on the priority right. (§105).

[5] The presumption also applies if the title to the subsequent application has not been acquired from the priority applicant but from a third party having the right to the invention in the respective territory (§106).

[6] The considerations leading to the presumption of priority entitlement apply to any case in which the subsequent applicant is not identical with the priority applicant but receives the support of the priority applicant required under Art.88(1) EPC. It does not matter whether the subsequent European application stems from a PCT application. It is also not relevant whether and to which extent the members of a plurality of co-applicants for the priority application overlap with the group of co-applicants for the subsequent application. (§107).

[7] The presumption should be rebuttable since in rare exceptional cases the priority applicant may have legitimate reasons not to allow the subsequent applicant to rely on the priority. (§108).

[8] Priority entitlement is not relevant before the priority is claimed by the subsequent applicant in accordance with Rule 52 EPC. Consequently, the presumption of entitlement exists on the date on which the priority is claimed and the rebuttal of the presumption must also relate to this date. (§109).

[9] Later developments cannot affect the rebuttable presumption. (§109).

[Court Note: Here, as of the filing date the inventors had assigned to BMS Pharma. That fact of itself must suffice to rebut the rebuttable presumption and require a more thorough-going assessment of title of the type that I have engaged in, reaching the conclusions that I have reached by reference to the foreign law evidence tendered.]

[10] The rebuttable presumption involves the reversal of the burden of proof, i.e. the party challenging the subsequent applicant's entitlement to priority has to prove that this entitlement is missing. (§110).

[11] If there is a strong presumption, the hurdle for rebutting it is higher than in the case of a weak presumption. The presumption that the subsequent applicant is entitled to the priority right is a strong presumption under normal circumstances since the other priority requirements (which establish the basis for the presumption of priority entitlement) can usually only be fulfilled with the consent and even cooperation of the priority applicant. (§110).

[12] The party challenging the entitlement to priority can thus not just raise speculative doubts but must demonstrate that specific facts support serious doubts about the subsequent applicant's entitlement to priority. (§110).

[Court Note: Though I have found that Delaware law favours BMS as regards the BMS argument, I accept that the facts to which my attention was drawn by Teva raised ostensibly serious doubts about BMS's subsequent entitlement to priority. So even taking BMS's case regarding the decision of the Enlarged Board of Appeal and saying 'yes, a rebuttable presumption arises', that presumption was rebutted to the extent that sufficiently serious were raised as to priority as to warrant a thorough-going examination of how priority lies in this case – albeit again that that further, thorough-going examination has yielded the conclusion that under the applicable law (the law of Delaware) the priority point falls, in my view, to be resolved in favour of BMS).]

[13] Like the priority entitlement in general, the presumption of its existence and the rebuttal of this presumption is subject to the autonomous law of the EPC only. Consequently, there is no room for the application of national laws on legal presumptions and their rebuttal. (§111).

9. Specific arguments forwarded during the referral proceedings in the context of question I

1233. Under the above heading the Enlarged Board made the following observations:

I. Legal certainty and uniform legal situation in the designated Contracting States

[1] The EPO is competent to assess priority entitlement. (§112).

[2] A rebuttable presumption in favour of the applicant's entitlement to priority is justified in view of the purpose of the priority rights, the lack of formal requirements for the transfer of priority rights and the presumed common interest of the priority applicant and the subsequent applicant (who have to cooperate when the priority is invoked). (§112).

[3] In the context of priority entitlement, the requirement of legal certainty would be best served if third parties could easily, based on publicly available data, assess whether the subsequent applicant is the successor in title addressed in Art.87(1) EPC. (§113).

[4] This assessment is difficult for third parties already because the relevant documents are normally non-public and in the possession of the applicant or patent proprietor only. (§113).

[5] The rebuttable presumption of priority entitlement serves the purpose of legal certainty insofar as the applicant or patent proprietor as well as third parties can or should rely on the subsequent applicant's entitlement to priority unless specific facts support serious doubts about such entitlement. (§113).

[6] The requirements of legal certainty and fairness in the individual case may conflict, and it may be argued that the presumption of a priority entitlement that is unjustified in a specific case disadvantages third parties, *i.e*. potential opponents. (In this context, the Enlarged Board observes that it should be considered that even if a 'wrong applicant' claims priority for its subsequent application, this does not necessarily mean that the priority right cannot be relied on). (§114).

[7] The EPC explicitly foresees the ex tunc assignment of priority rights, at least in the context of disputes on the right to the patent before national courts: if a person other than the original applicant is found to be entitled to the grant of the European patent, this person may choose to file a new European patent application in respect of the same invention under Article 61(1)(b) EPC, which new application filed by the rightful applicant under Article 61(1)(b) EPC is deemed to have been filed on the date of filing of the earlier application and to have the benefit of any right of priority. (§114).

[8] In view of legal certainty, it should thus be considered that there is always a party who is entitled to claim priority – even if this party must be determined in national proceedings. Consequently, third parties can never fully rely on the invalidity of a priority and on the potential invalidity of a patent which may result from such lack of priority entitlement. (§114).

[9] The EPO's competence to assess priority entitlement does not imply that national courts are bound by the EPO's assessments. In national proceedings concerning the validity of a European patent, relevant priority rights can be assessed taking into account all aspects, i.e. not only in view of the 'same invention' criterion but also with respect to priority entitlement. A uniform legal situation in all designated Contracting States can therefore never be guaranteed. (§115).

[Court Note: I note at this juncture, though, as I have previously noted, it is true generally of the decision of the Enlarged Board, that the Board consistently acknowledges the fact that national courts may need to apply national law in circumstances such as those now before me.]

[10] Challenges to priority entitlement before national courts are subject to national restrictions, regardless of how the EPO assesses priority entitlement. (§115).

II. Interest of third parties to challenge entitlement to priority

[1] Unlike disputes on the title to the patent application, in which normally only the applicant and other parties claiming rights to the invention are involved, challenges to the entitlement to claim priority are usually instituted by third parties, in particular by opponents. (§116).

[2] It is a matter of national law whether national courts should acknowledge a legitimate interest of a third party to obtain a decision on who is entitled to claim priority under Art.87(1) EPC. (§117).

[3] In the EPC, there are no restrictions on who can file an opposition. If the EPO is competent to assess all aspects of priority together with all patentability requirements ex officio in examination proceedings or on the request of an opponent, the EPO cannot refuse to assess a priority entitlement objection based on who raised the objection. (§117).

[4] The rebuttable presumption concerning priority entitlement however substantially limits the possibility of third parties, including opponents, to successfully challenge priority entitlement. (§117).

[Court Note: BMS, as I read its submissions, has contended that the decision of the Enlarged Board operates to exclude a priority challenge of the type that has been made by Teva in the present proceedings. If anything, points [1]-[4] seem to contemplate that third parties may and will bring challenges to a patentee's entitlement to priority. Of course, as the Enlarged Board contemplates at §117, the rebuttable presumption concerning priority entitlement would appear substantially to limit the possibility of third parties, including opponents, to successfully challenge priority entitlement. But that does involve the imposition of restrictions on who may file an opposition. In fact, the Enlarged Board makes quite clear that in the EPC, there are no restrictions on who can file an opposition, and that if the EPO is competent to assess all aspects of priority together with all patentability requirements ex officio in examination proceedings or on the request of an opponent, the EPO cannot refuse to assess a priority entitlement objection based on who raised the objection (see §117)].

10. Entitlement to priority in the context of PCT applications

1234. Under the above heading the Enlarged Board made the following observations:

I. The 'PCT joint applicants approach'

[1] The PCT joint applicants approach implies that in a PCT application where parties A and B are applicants for different designated States, both applicants may rely on the priority right derived from a priority application filed by only one of the applicants, without the need for any transfer of priority rights. (§118).

[2] However, a general decision on the viability of the PCT joint applicants approach is not needed. The concept of an implied agreement should allow an assessment leading to the same result as the PCT joint applicants approach in most cases. (§121).

II. The concept of an implied agreement

[1] Where no formal requirements for the transfer of priority rights exist, priority rights can be transferred under an informal or implicit agreement. (§122).

[2] In the absence of clear indications to the contrary, the joint filing of the subsequent PCT application sufficiently proves that the parties entered into an implied agreement allowing party B to rely on the priority right established by the filing of the priority application by party A. (§125).

[3] Since the considerations leading to point [2] not only apply in the context of PCT applications, the concept and the conditions for an implied agreement equally apply to co-applicants directly filing a subsequent European application if at least one of the co-applicants was an applicant for the priority application. (§125).

[4] To put into question the implied agreement, evidence would be needed that an agreement on the use of the priority right has not been reached or is fundamentally flawed.

[5] Factual indications putting into question the implied agreement have to be of a substantial nature and have to be presented by the party questioning the implied agreement. (§126).

[6] The implied agreement is to be assessed under the autonomous law of the EPC, which does not foresee any formal requirements for the transfer of priority rights. Assessing the existence of an implied agreement under the autonomous law of the EPC is consistent with the approach chosen for the rebuttable presumption for the priority entitlement and appropriate in view of the object of the implied agreement, which is governed by the EPC and the Paris Convention only. (§126).

[7] Transfers of private rights and underlying agreements are normally subject to national civil laws, but there are instances where the EPC regulates aspects of national civil laws in order to establish uniform standards. In this context, the Enlarged Board of Appeal considered it justified to consider the agreement implied by the joint filing of a subsequent application to be an agreement governed only by the autonomous law of the EPC. (§127).

[8] An agreement (regardless of form) can only be held against parties who were involved in the facts establishing the agreement. Co-applicants for the priority application who were not involved in the subsequent application may not be deemed to have consented to the reliance on the priority right by the other co-applicants for the priority application. The subsequent applicant(s) may however still be entitled to claim priority since the rebuttable presumption of entitlement does not depend on whether the involved applicants acted as co-applicants at any stage. (§128).

11. Implications for the referred questions

1235. Under the above heading the Enlarged Board turned to a consideration of the referred questions by reference to its preceding analysis, making, amongst other matters, the following points:

I. Question 1 – Competence of the EPO to assess priority entitlement

[1] The subsequent applicant wishing to file a European patent application should not only hold the title to that European application (*i.e.* the right to the European patent) but also the priority right if such right is claimed for the European application. (§129).

[2] In the context of the EPC and the proceedings before the EPO, a strict distinction should be made between the two rights: (i) the title to the subsequent application, on the one hand, is subject to national property laws; its transfer is governed by national laws and assessed by national courts; (ii) the right to claim the priority date for the subsequent European application, on the other hand, is a right created under the autonomous law of the EPC and the Paris Convention, the transfer of which should also be assessed under the autonomous law of the EPC. (§129).

[Court Note: I note that the decision is confined to proceedings before the EPO and that the issue of title to the subsequent application is a matter for national law.]

[3] The exclusive application of the autonomous law of the EPC to the transfer of priority rights removes the need for conflict of laws rules and the application of national laws, thereby eliminating two main reasons invoked against the EPO's competence to assess whether a party is entitled to claim priority under Article 87(1) EPC. (§130).

[4] The EPO is competent to assess priority entitlement. (§130).

[5] In view of the interests of the parties involved, the lack of formal requirements for the transfer of priority rights and the necessary cooperation between the priority applicant and the subsequent applicant in the context of the procedural requirements under Art.88(1) EPC, the entitlement to priority should be presumed to exist. (§131).

[6] This presumption should be rebuttable to take into account rare exceptional cases in which the claiming of the priority by the subsequent applicant appears to be unjustified. (§131).

[7] If the requirements under Article 88(1) EPC are not fulfilled, the subsequent applicant is barred from claiming priority for this reason alone. (§132).

[8] The fulfilment of these procedural requirements is not covered by the rebuttable presumption. (§132).

[9] Like the nature and the effects of the priority right and the entitlement to priority, the rebuttable presumption in favour of the priority entitlement is subject to the autonomous law of the EPC. It cannot be excluded, however, that in the context of the rebuttal of the presumption national laws need to be considered as well. (§133). "*For example, the existence of legal entities being parties in transfers of priority rights may be relevant and may need an assessment under national laws*" (§133).

[Court Note: Again, §133 lends support to the approach that I have adopted in this case when it comes to resolving the priority issue.]

II. Question 2 – Priority entitlement in the situation addressed in question II

[1] The Enlarged Board leaves open the validity of the 'PCT joint applicants approach' but endorses the concept of an implied agreement. (§136).

[2] In the absence of substantial factual indications to the contrary, the joint filing of the subsequent PCT application sufficiently proves that the parties entered into an implied or informal agreement allowing party B to rely on the priority right established by the filing of the priority application by party A. (§136).

[3] An agreement cannot be implied if not all of a plurality of priority applicants are applicants or co-applicants for the subsequent application. (§137).

[4] However, the rebuttable presumption of priority entitlement can be applied also in situations where one of the priority applicants is not involved in the filing of the subsequent application. (In specific contexts, a priority applicant missing from the subsequent application may have reasons to claim the title to the subsequent application (in proceedings before national courts) or may possess evidence to rebut the presumption of priority entitlement in proceedings before the EPO. (§137).

[5] The interpretation of a joint filing as sufficient proof for an implied agreement on the joint use of the priority right in the context of a joint PCT application may apply independently from the rebuttable presumption addressed in connection with referred question I. (§138).

[6] An implied agreement in the situation addressed in question II can reinforce the presumption of entitlement to priority stipulated in view of referred question I. (§138).

12. Conclusion

1236. As indicated above, the Enlarged Board of Appeal concluded as follows:

1. The European Patent Office is competent to assess whether a party is entitled to claim priority under Art.87(1) EPC.
2. There is a rebuttable presumption under the autonomous law of the EPC that the applicant claiming priority in accordance with Art.88(1) EPC and the corresponding Implementing Regulations is entitled to claim priority.
3. The rebuttable presumption also applies in situations where the European patent application derives from a PCT application and/or where the priority applicant(s) are not identical with the subsequent applicant(s).
4. In a situation where a PCT application is jointly filed by parties A and B, (i) designating party A for one or more designated States and party B for one or more other designated States, and (ii) claiming priority from an earlier patent application designating party A as the applicant, the joint filing implies an agreement between parties A and B allowing party B to rely on the priority, unless there are substantial factual indications to the contrary.

C. Some Observations

1237. I do not have a great deal to add to the notes that I inserted above as I proceeded with my consideration of the Enlarged Board's decision.

1238. The decision of the Enlarged Board of Appeal in Consolidated Cases G0001/22 and G0002/22 undoubtedly represents a significant evolution of the law applicable to patent applicants who go before the European Patent Office – and the decision is confined to proceedings before the EPO (see §129).

1239. The prospect that applicants before the EPO will now face opposition challenges to the right to claim priority must now be greatly reduced. That said, while the EPO may presume that a priority claim is valid, I do not see anything in that which suggests that there has been some attenuation of the position pertaining in national courts as to the documents required to show a clean chain of title (and an associated transfer of priority rights).

1240. In this last regard, I would make a trio of associated points. First, where (as here) questions of entitlement to claim priority under Art.87(1) of the EPC arise in national proceedings, the court seised continues to need to address all issues concerning the applicant's identity or succession,

including the determination and application of foreign laws in accordance with its own conflict of laws rules (§70). Second, in the context of the rebuttal of the presumption, that applicable foreign law may need to be considered (§133). Third, the presumption identified by the EPO is in any event rebuttable and here sufficient doubt was raised by Teva to overcome the presumption and to lead me to engage in the further consideration of the priority issue that I undertook in the earlier part of this judgment (which further consideration has led me to conclude by reference to Delaware law that the law of Delaware favours BMS on the priority point).

D. Conclusion

1241. As will be clear from my analysis of the priority point in previous chapters, I do not accept that Teva's priority challenge should succeed, for the reasons that I have stated in those previous chapters. I do not see anything in the decision of the EPO's Enlarged Board of Appeal in Consolidated Cases G0001/22 and G0002/22 that would alter my view in this regard.

XIV. FINAL CONCLUSIONS

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Conclusions

1242. It follows from the preceding chapters that:

1. Irish Patent Number EP (IE) 1 427 415 is not valid, but

2. by virtue of Delaware law, if it was valid (and it is not) it would enjoy its presently claimed priority date.

APPENDIX 1

Abridged Written Evidence of Mr Chandler[17]

Statement #1 of 2

"*My Opinion*

1. *I agree with and adopt Justice Holland's statement of Delaware law and the analysis set forth in the Holland Expert Report. Applying that analysis to the facts provided by the Golian Statement, I reach the same conclusions as Justice Holland reached in the Holland Expert Report.*
2. *Specifically, as explained in the Holland Expert Report, it is settled law that, while Delaware generally recognizes the separate and independent existence of wholly- owned subsidiaries, those formalities are set aside in certain instances. Delaware statutory law has codified that principle when considering a parent corporation's ability to exercise actual control over its subsidiary's assets and operations. Delaware cases have confidently affirmed that – given the practical and operational benefits that a wholly-owned subsidiary affords the parent – the subsidiary is expected to operate solely for the parent corporation's benefit. As a result, the parent corporation may direct and control the subsidiary's actions. Applying these principles in view of BMS Co's 100% ownership of BMS Pharma, I agree with Justice Holland that BMS Co had the right to cause its wholly owned subsidiary to assign to BMS Co the right to claim priority from the first-filed patent application.*
3. *Further, Justice Holland fully and accurately described the distinction between 'beneficial' title and 'legal' title under Delaware law. While one party may hold legal title to an asset, the asset's beneficial owner is the ultimate decision maker. Similarly to Justice Holland, I would conclude from the Golian Statement that BMS co-established a practice of resting legal ownership of certain intellectual property assets with its wholly-owned subsidiaries, including in particular BMS Pharma, while retaining beneficial ownership of, and its attendant control over, those assets. Mr. Golian's employment post-dated BMS Co's adoption of that policy, and he was not part of the 24 October 2001 email chain which described it. However, that policy was in place when he commenced employment with BMS Co the following year, and he was aware of it, and he has stated that it reflects his experience of BMS Co being the decision maker and having control over how the intellectual property assets of its wholly-owned subsidiaries are to be held and managed. Furthermore, the Golian Statement confirms that BMS Co's policy described above and its attendant control over BMS Pharma's intellectual property assets remained the state of affairs as of the date of the later-filed patent application.*
4. *In my opinion, a Delaware Court would conclude the same. See, e.g., Lynch v. Gonzalez, 2020 WL 4381604, at *31-33 (Del. Ch. July 31, 2020) (concluding from the parties' practices and conduct that they established an*

[17] This abridged version of Mr Chandler's evidence contains his two statements and also the statement of Mr Holland and Ms Marla Mathias (the latter two documents being appended to Mr Chandler's initial statement). I have not included the texts of the cases that were appended to the opinion and to which I make reference, where and as appropriate, elsewhere in my judgment.

*implicit agreement by which one held the legal title to the controlling ownership interest in the subject company, but the other retained beneficial ownership and its attendant control), aff'd, 253 A.3d 556 (Del. 2021); Taylor v. Jones, 2002 WL 31926612, at *3 (Del. Ch. Dec. 17, 2002) (explaining that separation of beneficial and legal title is found where 'it is intended that one party will hold legal title to property for the benefit of another party who has equitable or beneficial ownership of that property'); Cartanza v. Lynn, 2002 WL 31007802, at *2 (Del. Ch. Aug. 8, 2002) (explaining that separation of beneficial and legal title is 'imposed in circumstances where the intent was for one party to hold legal title to property on behalf of another party having equitable or beneficial ownership of that property,' and that such a determination 'arises from the presumed intention of the parties and the circumstances of that particular transaction'); Danvir Corp. v. Wahl, 1987 WL 16507, at *6 (Del. Ch. Sept. 8, 1987) (explaining that separation of beneficial and legal title will be 'implied by law where the circumstances indicate that the party holding legal title was not intended to have any beneficial interest in the property'). Thus, I agree with Justice Holland's conclusion that BMS Co could be characterized as the beneficial owner of the earlier-filed patent application….*

Expert Report of Mr Holland, as appended to the first opinion of Mr Chandler

....FACTS PROVIDED BY WILMERHALE

1. *The present case concerns a patent application filed on September 17, 2002 by Bristol- Myers Squibb Company ('BMS'). This claimed priority from a first patent filing made on September 21. 2001, by two employees of what was at the time DuPont Pharmaceuticals Company, but which was renamed Bristol-Myers Squibb Pharma Company on its acquisition by BMS from E.I. DuPont de Nemours and Company on October 1, 2001. On such acquisition Bristol-Myers Squibb Pharma Company became an indirectly but wholly owned subsidiary of BMS….*
2. *All these corporate entities were incorporated under Delaware law, the ultimate subsidiary Bristol-Myers Squibb Pharma Company being a partnership under Delaware law. the partnership structure having been a consequence of DuPont Pharmaceuticals Company having previously been a JV between DuPont and Merck.*
3. *The two DuPont Pharmaceuticals Company employee inventors executed an assignment of the first patent filing in favor of Bristol-Myers Squibb Pharma Company on November 3, 2001 and at around the same time entered into employment agreements with BMS, as part of the integration of the operations of Bristol-Myers Squibb Pharma Company into BMS.*
4. *No written assignment in the 2001-2002 timeframe from Bristol-Myers Squibb Pharma Company to BMS of the right to claim priority from the first patent filing has been located. After extensive searches, the only internal documentation at the time that has been located and that expresses a policy as to patent ownership is an email chain late in October 2001 which states (in so far as relevant to the present situation, the other two categories relating to other businesses that had been acquired at the same time):*

'We have determined the following 3 categories of 'DuPont Pharma patents and trademarks, based on the business to which the intangibles relate....

(1) Patents and trademarks related to the pharmaceutical business - Maintain legal ownership in Bristol-Myers Squibb Pharma Company (formerly DPC). We believe that this is the entity where they currently reside so this should involve only a name change. New patents and trademarks in the name of Bristol-Myers Squibb Company.'

5. *Marla Mathias, Vice President and Chief Patent Counsel at BMS, until she left in November 2001, having stayed on to integrate the patent operations of DuPont Pharmaceuticals Company into those of BMS, and the person in the BMS patent department most closely involved with the acquisition and the integration. This email was forwarded to her. She has confirmed that this was to her the natural way of dealing with matters and that there was nothing surprising or exceptional about this approach (quoting from her approved statement):*

'We did not take any steps to transfer legal title to the patents and patent applications held by what was by then Bristol-Myers Squibb Pharma Company to BMS. It was a no-brainer to leave them where they were as we had access to them anyway so why go the effort of assigning them? There was no need to transfer legal title, and it would have made no sense to do so, as BMS was able in effect to treat Bristol-Myers Squibb Pharma Company as a bucket out of which the intellectual property rights which it held at the closing could be withdrawn as necessary or otherwise deployed.'

LEGAL BACKGROUND PROVIDED BY WILMERHALE

6. *One fundamental aspect of the international patent system is that someone seeking a patent needs initially only to file the one patent application in a country that is party to the Paris Convention for the protection of industrial property (in practice nearly all countries are parties to it). Such applicant may then, provided that it does so within one year of that first filing, make patent filings based on that first filing in, or in respect of, other countries, which 'claim priority' from such first filing and which are accordingly deemed to have been filed in such other countries on the date when the first filing was made. This means that the 'state of the art; by which attacks on patent validity on the technical grounds of lack of novelty and lack of inventive step (obviousness) are determined in such other countries is the date of first filing in the initial country of filing, and not the actual filing date in those other countries. The new technical art which becomes available in the course of that year can make all the difference to the strength of such technical attacks, which is why it is critical for a patentee in most cases to be able to establish that priority was properly claimed. Were it not for such a mechanism, a prospective patentee would have to file patent applications simultaneously, and at the very outset, in all the countries in which it might wish to secure patent protection.*
7. *The Paris Convention also allows priority to be claimed by 'successors in title' without however elaborating on that term. It is common for the entity*

making the later filings and the claim to priority to be a successor in title to the first applicant. This used particularly to be the case with first US filings as it used to be necessary to file these in the names of the inventors rather than, as is usual in Europe, their employer.

8. *What constitutes a 'successor in title' has become important in European patent litigation in recent years because national courts in Europe, here following the practice of the European Patent Office as confirmed by its Boards of Appeal, have held that the right of a successor in title to claim priority must be assigned to it before it makes such claim to priority, and cannot be perfected by an assignment made after such claim has been made. There have been a number of cases, particularly in the European Patent Office. but also some in national courts, where third parties, seeking to challenge the validity of a granted patent, have successfully attacked the right to claim priority on the basis that, when making the later filing, the patent applicant did not have the right to make such a claim. An English example of such a case is provided by Edwards Life Sciences AG v. Cook Biotech Inc. [2009] EWHC 1304 at [82]-[100].*

9. *Patent offices and courts in jurisdictions outside Europe do not take such a strict view and, recognizing that such an attack is something of a technicality that has nothing to do with the underlying merits of patent disputes, national courts in Europe have devised various ways to lessen the rigor of this approach. The English courts have done so by recognizing that a patent applicant may be a successor in title by virtue of beneficial ownership, as in Fujifilm Kyowa Kirin Biologics Company Ltd. v. AbbVie Biotechnology Ltd. [2017] EWHC 395 at [16] to [98]. The German and Dutch courts have taken similar approaches.*

QUESTIONS PRESENTED

10. *On the basis of the above outline of legal background and facts, WilmerHale sought my expert opinion as to whether, as a matter of Delaware law, BMS, when it filed the later patent application in 2002, by virtue of its 100% ownership of its subsidiary Bristol-Myers Squibb Pharma Company, and its stated internal policy as to patent filings:*

    (1) had the unfettered right to call for such subsidiary to assign to BMS the right to claim priority from the earlier filed patent application, such that it could be treated as a successor in title to such subsidiary under the Paris Convention as that term has been interpreted by the English courts.

    (2) could be characterized as the beneficial owner of the earlier filed patent application.

ANSWERS AND ANALYSIS

<u>QUESTION ONE LEGAL ANALYSIS</u>

11. *As a general principle of Delaware law, a corporation is viewed as a separate legal entity, independent from its stockholders, directors, and officers as well as its parent, subsidiaries, and affiliates. Accordingly, stockholders are ordinarily at risk of losing only their equity investment in the corporation.[1] Limitation of liability is an important incentive for the formation of, and investment in, corporations.[2]*

12. *Corporations routinely conduct operations that carry separate risks of*

liability through separately incorporated subsidiaries. The principle of limited liability applies to any stockholder, whether individuals or corporations.[3] It also applies where one corporation (the parent corporation) owns all or a majority of the stock of one or more corporations (referred to as subsidiaries). One frequent model is when a parent corporation owns all the stock of one or more subsidiaries-in which case each subsidiary is wholly owned by the parent.

13. *In Hollinger, Inc. v. Hollinger International, Inc., the Delaware Court of Chancery acknowledged that public companies frequently conduct their operations through wholly owned subsidiaries. It noted that ' they do this for reasons that are perfectly legitimate. These include the desire to limit liabilities to third parties involved in operating certain business lines to those lines and to minimize tax liability.'[4]*

14. *In Hollinger. the Court of Chancery pointed out the fact that Delaware 'law recognizes the separate existence of wholly owned subsidiaries for [legitimate] purposes like this does not necessarily mean that it should recognize their separate existence for all purposes' The Court of Chancery rejected the argument that 'a wholly owned subsidiary is either without any legal dignity at all in the sense that it fails the severe test required to pierce the corporate veil or else its separate existence must be recognized in all contexts.'[5]*

15. *In doing so, the Court of Chancery stated that this binary approach 'does not comport with the approach Delaware has taken in other areas of its corporate law. It creates a Hobson's choice that [is] unnecessary.'[6] In Hollinger, the Court observed the distinctive considerations that apply to the relationship between a parent corporation stockholder and wholly owned subsidiary corporations 'within the corporate family' can be recognized under Delaware law 'without doing violence to the wealth-creating value of limiting the ability of third parties who deal with wholly owned subsidiaries to seek recourse against parent corporations.'[7]*

16. *An amendment to the Delaware General Corporation Law statute (the 'DGCL') is a good example of a distinctive consideration that applies to the relationship between parent corporations and wholly owned subsidiaries. In 2003, Section 220 of the DGCL was amended to require the production by a parent of its subsidiary's books and records to the extent that the parent ·'corporation could obtain such records through the exercise of control over such subsidiary...'.[8] In Weinstein Enterprises, the Delaware Supreme Court interpreted that provision in the amended statute to mean that such power could only be exercised by the parent corporation over a wholly owned subsidiary.[9] The synopsis to that 2003 amendment stated that it was 'not intended to affect existing legal doctrine that, as a general matter, respects the corporate existence of subsidiaries in relation to liability of stockholders to third parties, personal jurisdiction over subsidiaries of Delaware corporations, and discovery in litigation other than under Section 220.'[10]*

17. *Another example of Delaware law recognizing the distinctive considerations that apply to the relationship between parent corporations and wholly owned subsidiaries is in Section 271 of the DGCL. Effective August 1, 2005, the Delaware General Assembly amended Section 271 to add a new subparagraph (c) (the 'Amendment'). which provides as follows:*

> *(a) For purposes of this section only, the property and assets of the corporation include the property and assets of any subsidiary of the*

> *corporation. As used in this subsection, 'subsidiary' means any entity wholly owned and controlled, directly or indirectly, by the corporation and includes, without limitation, corporations, partnerships, limited partnerships, limited liability partnerships, limited liability companies, and/or statutory trusts. Notwithstanding subsection (a) of this section, except to the extent the certificate of incorporation otherwise provides, no resolution by stockholders or members shall be required for a sale, lease or exchange of property and assets of the corporation to a subsidiary.*

18. *In the synopsis relating to the Amendment, the Delaware General Assembly described the purpose of the amendment as follows:*

> *Section 271 has been amended to add new subsection (c). The purpose of subsection (c) is to provide that (i) no stockholder vote is required for a sale, lease or exchange of assets to or with a direct or indirect wholly owned and controlled subsidiary, and (ii) the assets of such a subsidiary are to be treated as assets of its ultimate parent for purposes of applying, at the parent level, the requirements set forth in subsection (a). The amendment is not intended to address the application of subsection (a) to a sale, lease or exchange of assets by, or to or with, a subsidiary that is not wholly owned and controlled. directly or indirectly. by the ultimate parent.*

19. *The directors of Delaware corporations have fiduciary duties to the corporation and its stockholders.*[11] *In Anadarko Petroleum Corp. v. Panhandle E. Corp., more than thirty years ago. the Delaware Supreme Court held that 'a parent [corporation] does not owe a fiduciary to its wholly owned subsidiary.'*[12] *This holding is a 'settled principle of Delaware law'.*[13]

20. *In its seminal Anadarko opinion, the Delaware Supreme Court held 'in a parent and wholly owned subsidiary context, the directors of the subsidiary are obligated to only manage the affairs of the subsidiary in the best interest of the parent and its shareholders.'*[14] *The holding in the Court of Chancery decision that was affirmed by the Delaware Supreme Court in Anadarko explained that the parent-subsidiary relationship meant 'that there need be no consideration for a transfer of assets between the companies.'*[15]

21. *'Wholly owned subsidiary corporations are expected to operate for the benefit of their parent corporations; that is why they are created.'*[16] *When a parent corporation directs the fiduciaries (directors) of a wholly owned subsidiary to take action that is in the best interest of the parent. the separate legal existence of the corporations is not compromised. This was explained by the Delaware Supreme Court in Lambrecht v. O'Neal.*[17]

22. *That case involved a merger that resulted in Merrill Lynch becoming a wholly owned subsidiary of Bank of America Corporation (BofA). The issue in the case was standing to bring Merrill Lynch's pre-merger derivative claims. The Delaware Supreme Court held 'BofA's sole ownership alone and without more, empowers and entitles BofA, acting through its own board of directors or authorized officers, to use its direct control to cause its wholly owned subsidiary, Merrill Lynch, to do what is necessary to*

enforce Merrill Lynch's pre-merger claim."[18] The Delaware Supreme Court stated that this result would not 'disrespect the status of Merrill Lynch as a separate entity or constitute a de facto piercing of the corporate vei1."[19] In addition, the Supreme Court stated that 'Merrill Lynch's corporate separateness would not be diminished by action taken by its sole owner directing Merrill Lynch's managers to file a lawsuit."[20]

QUESTION ONE ANSWERED

23. *On the basis of the foregoing analysis of Delaware law, it is my expert opinion that, as a matter of Delaware law, when BMS filed the later patent application in 2002, by virtue of its 100% ownership of its subsidiary Bristol-Myers Squibb Pharma Company, and its stated internal policy as to patent filings, BMS had the unfettered right to call for such subsidiary to assign to BMS the right to claim priority from the earlier filed patent application. Therefore, BMS could be treated as a successor in title to such subsidiary under the Paris Convention, as I understand that term has been interpreted by the English courts, according to the cases cited in the legal background provided to me.*

QUESTION TWO LEGAL ANALYSIS

24. *The legal analysis of Delaware law in Paragraphs 21 to 33 is equally applicable to the answer to Question Two and is relied upon in its entirety in answering Question Two.*

25. *The term 'beneficial ownership' is commonly understood to encompass the notion of having the 'true ownership' interest but with 'the legal title held by another."[21] 'Equitable title' is an alternative term for "beneficial title. This settled principle of Delaware law applies to any asset whenever there is a separation of 'true ownership' and legal title. It occurs frequently with stock in a Delaware corporation that is traded on a public exchange.[22]*

26. *In Anadarko, the Delaware Supreme Court explained that the concept of 'beneficial ownership' of stock, though somewhat inexact, is contextually defined, and has become a term of art for purposes of establishing fiduciary duties under Delaware law.[23] As applied in the stock context. beneficial ownership contemplates a separation of legal and equitable ownership. Under this concept, the equitable or beneficial owner possesses an economic interest in the subject property distinct from legal ownership.[24] The Delaware cases are clear, however. that the term 'beneficial owner' necessarily includes the right to direct how their shares will be voted by the holder of legal title and to expect to receive duties of loyalty and due care from the holder of legal title, who is acting in a fiduciary capacity for the beneficial owner.[25]*

QUESTION TWO ANSWERED

27. *The foregoing legal analysis regarding the beneficial ownership of stock applies when determining the beneficial ownership of any asset of a corporate entity. The facts provided reflect that BMS decided to hold legal title to the patent in the name of its wholly owned subsidiary, Bristol-Myers Squibb Pharma, pursuant to its internal policy as to patent filings, which treated Bristol-Myers Squibb Pharma as 'a bucket out of which intellectual property rights which it held at the closing could be withdrawn as necessary or otherwise deployed."[26]*

28. *The directors of a wholly owned Delaware subsidiary corporation are obligated to only manage the affairs of the subsidiary in the best interest of the parent and its shareholders."[27] BMS had and has the absolute right to direct the legal title holder of the patent, Bristol-Myers Squibb Pharma Company, to take any and all action regarding the patent that is in the best interest of BMS.*

29. *On the basis of the foregoing analysis of Delaware law, it is my expert opinion that, as a matter of Delaware law, when BMS filed the later patent application in 2002, by virtue of its 100% ownership of its subsidiary Bristol-Myers Squibb Pharma Company, and its stated internal policy as to patent filings, BMS could be characterized as the beneficial owner of the earlier filed patent application….*

[Footnotes]

1 *BASF Corp. v. POSM fl Props. P'S, l.P. 2009 WL522721 at *8 n. 50. (Del. Ch. Mar. 3, 2009).*

2 *AllianceData vs.Corp.v. Blackstone Capital Partners V F.P., 963 A.2d 746, 769 (Del. Ch. 2009) ('A huge amount of wealth generation results from the use of distinct entities by corporate parents to conduct business. This allows parents to engage on risky endeavors precisely because the parent can cabin the amount of risk they are taking by using distinct entities to carry out certain activities. Delaware law respects corporate fonnalities, absent a basis for veil-piercing, recognizing that the wealth-generating potential of corporate and other limited liability entities would be stymied if it did otherwise.').*

3 *Buechner v. Farbenfabriken Bayer Aktiengesellschaft, 154 A.2d 684, 686-87 (Del. Ch. 1959) (citing Bird v. Wilmington Soc. of Fine Arts, 43 A.2d 476 (Del. 1945)).*

4 *Hollinger, Inc. v. Hollinger International, Inc., 858 A.2d 342, 347 (Del. Ch. 2004).*

5 *Id. at 374-75.*

6 *Id. at 375.*

7 *Id.*

8 *8 Del. C. § 220(b).*

9 *Weinstein Enterprises v. Orloff, 870 A2d 479 (Del. 2005).*

10 *S.B. No. 127, 142d General Assembly, 74 Del. Laws Ch. 84 (2003).*

11 *Aronson. Lewis, 473 A.2d 805 (1984); Loft v. Guth, 2 A.2d 225 (Del. Ch. 1938), affd Del. Supr., 5 A.2d 503 (1939).*

12 *Anadarko Petrol. Corp. v. Panhandle E. Corp., 545 A.2d 117I (Del. 1988).*

13 *TrenwickAm. litig Tr. r. Ernst & Young. L.l.P., 906 A..2d 168, 191 (Del. Ch. 2006).*

14 *Anadarko, 545 A.2d 1171; In 2020, the Court of Chancery cited that settled principle of Delaware law from Anadarko and reiterated that if the parent corporation determines that certain actions are 'desirable for the parent' the subsidiary fiduciaries (directors) 'are obligated to only manage the affairs of the subsidiary in the best interests of the parent and its shareholders.' The Chemours v. DowDupont, 2020 Del. Ch. LEXIS 112. In Chemours, the parent corporation directed the wholly owned subsidiary to execute an arbitration agreement. On December 15, 2020, the Delaware Supreme Court affirmed that Court of Chancery judgment in a unanimous one sentence en bane order 'on the basis of and for the reasons stated in its March 20, 2020 memorandum opinion.'*

15 *Anadarko Petrol. Corp. v. Panhandle E. Corp., 1987 WL 16508 (Del. Ch. Sept. 8, 1987) at *4.*

16 *Trenwick, 906 A. 2d 168, 173.*

17 *Lambrecht v. 0 'Neal, 3 A.3d 277 (Del. 20 I0).*

18 *Lambrecht, 3 A.3d 277 at 290.*

19 *Id.*

20 *Id. at 289 fu. 40.*

21 *CME Group Inc. v. Chi. Bd. Options Exch., 2009 WL 1856693, at *5 (Del. Ch. June 25, 2009).*

22 *See, e.g., In re Appraisal of Dell, Inc., 143 A.3d 20, 23 (Del. Ch.2016).*

23 *See Sundlum v. Executive Jet Aviation, Inc., 273 A.2d 282, 285 (Del. Ch. 1970).*

24 *Id.*

25 *Mangano v. Pericor Therapeutics. Inc., 2009 Del. Ch. LEXIS 197 (citing Anadarko, 545 A.2d at 1176).*

26 *See Paragraph 16.*

Statement of Ms Marla Mathias,
as appended to the opinion of Mr Holland

(1) *I am a US qualified attorney, admitted to practice at the New York Bar and before the US Patent and Trademark Office. I was from June 1999 until November 15, 200 I employed by Bristol-Myers Squibb Company ('BMS'), toward the end as Vice President and Chief Patent Counsel. In the several month period before I left BMS I worked on the acquisition by BMS from E. l. Du Pont De Nemours and Company of its subsidiary DuPont Pharmaceuticals Company. I have been asked to set out my recollections of that acquisition (which I have been told was the subject of a purchase agreement dated June 7, 2001 which closed on October l, 2001) and the initial steps that were taken to integrate the patent estate and patent operations of DuPont Pharmaceuticals Company (which I am told was renamed Bristol-Myers Squibb Pharma Company) into BMS.*

(2) *I recall it being a big acquisition for BMS, and a lot of in-house people at BMS working on it - indeed I vividly remember being on a call with some 30 to 40 people who were also working on it on when we learned of the September 11, 200 I terrorist attacks. Having already told BMS that I would be leaving, I had been asked to stay on for a while to be part of that team as the person most responsible for a number of the patent-related aspects of the transaction. As part of this, before the closing, I went to the DuPont Pharmaceuticals Company facility in Wilmington, Delaware together with our docketing clerk, Dora Lynch. Our purpose in so doing was not only to undertake due diligence on their intellectual property assets, but also to identify those held elsewhere in E. I. Du Pont De Nemours and Company for which licenses might be required after the closing. We had also to review their patent docketing arrangements and renewal systems so that, after the closing, BMS would be able to integrate the management of the patents held by DuPont Pharmaceuticals Company into BMS's own system. As part of this I also met with patent attorneys at DuPont Pharmaceuticals Company, including those who would join BMS after the closing. I also attended meetings at Cravath, Swaine & Moore, our external lawyers on the transaction, to discuss issues such as which entity should hold, and which should*

have a license to, those patents that were of interest to both BMS and E. I. Du Pont De Nemours and Company.

(3) After the closing, one of the main activities that I undertook was to supervise the integration of the patent docketing and renewals arrangements of what was by then Bristol-Myers Squibb Pharma Company into those of BMS. A vast amount of work went into this. My aim here was to set things up before I left so that others could pick up the ball and run with it. We did not take any steps to transfer legal title to the patents and patent applications held by what was by then Bristol-Myers Squibb Pharma Company to BMS. It was a no-brainer to leave them where they were as we had access to them anyway so why go the effort of assigning them? There was no need to transfer legal title, and it would have made no sense to do so, as BMS was able in effect to treat Bristol-Myers Squibb Pharma Company as a bucket out of which the intellectual property rights which it held at the closing could be withdrawn as necessary or otherwise deployed. Another way of describing how Bristol-Myers Squibb Pharma Company was seen as holding such intellectual property is set out in an email of October 19, 2001 from Robert Souka to Francis Rossi which I have been shown (I was not copied in on it and so would not have seen it at the time). This states that 'BMS Pharma Company houses most of the intangibles, the acquired sites and realty (...) and pharmaceutical operations formerly operated by DuPont.' (emphasis added)

(4) My recollection of how we dealt with the intellectual property rights which Bristol- Myers Squibb Pharma Company held as at the closing is also confirmed by an email which I have been shown and which was forwarded to me, and others, by Mark Sobecki on October 29, 2001, shortly before I left BMS. One of the other recipients was the late David Bonk, who was my direct manager and, as I understand, took over my responsibilities after I left. The email had been copied to Mark Sobecki by Francis Rossi on October 24, 200 I. This email noted:

> *We have determined the following 3 categories of 'DuPont Pharma' patents and trademarks, based on the business to which the intangibles relate. Please let us know if any of our recommendations for legal entity registration of these intangibles doesn't make sense from your perspective (I include cc's in that request) - (I) Patents and trademarks related to the pharmaceutical business - Maintain legal ownership in Bristol-Myers Squibb Pharma Company (formerly DPC). We believe that this is the entity where they currently reside, so this should involve only a name change. New patents and trademarks in the name of Bristol-Myers Squibb Company.*

The email then went on to discuss at (2) and (3) two other businesses that had been acquired from DuPont along with DuPont Pharmaceuticals Company but as to which more complex arrangements were necessary, in one case because the business was to be sold. I am pretty sure that not only would I would have been involved in the discussions which led to these decisions, but that this email was memorializing decisions and planning that had been

underway since June, and as my manager, Dave Bonk would have overseen these decisions. For the reasons l have given above, leaving everything related to the pharmaceutical business in Bristol-Myers Squibb Pharma Company was not a memorable decision, and had surely been the default one from nearly the beginning of our due diligence. I can't think of any reason why one would have done it any other way. In contrast the focus of discussion would have been on how to handle the intellectual property rights that related to the other two businesses. As for the statement '[n]ew patents and trademarks in the name of Bristol-Myers Squibb Company', this would have reflected the integration of the ongoing activities of DuPont Pharmaceuticals Company into those of BMS, and so one would expect subsequent patent filings to be made in the name of BMS….

Statement #2 of 2 of Mr Chandler

Introduction

1. *I submit this supplemental statement to address certain issues raised in the Expert Statement of Myron T. Steele, dated 14 April 2022 (the 'Steele Report'), and in further support of the expert report of my recently deceased colleague, Randy J. Holland, dated 29 June 2021 (the 'Holland Report') and my own expert statement, dated 12 April 2022 (my 'Initial Statement')….*

Comments on the Steele Report

2. *I agree with Chief Justice Steele's recognition that BMS Co and BMS Pharma are separate legal entities under Delaware law and that Delaware generally protects corporate separateness. I disagree with Chief Justice Steele's conclusion that BMS Co does not control the patent held by BMS Pharma. Contrary to Chief Justice Steele's comments, the Delaware cases and statutes cited in the Holland Report are instructive and support my conclusions and Justice Holland's conclusions.*

<u>The Hollinger Case</u>

3. *Chief Justice Steele criticizes Justice Holland's reliance on Hollinger Inc. v. Hollinger International, Inc., 858 A.2d 342 (Del. Ch. 2004), for the proposition that just because 'the law recognizes the separate existence of wholly owned subsidiaries for [legitimate] purposes . . . does not necessarily mean that it should recognize their separate existence for all purposes.' Id. at 374; see Holland Report ¶¶ 24–26. Chief Justice Steele contends this statement in Hollinger was dicta and should not be relied upon to interpret Delaware law. See Steele Report ¶ 24. But, Chief Justice Steele overlooks the importance of the proposition to the Hollinger court's analysis and ultimate decision.*
4. *In Hollinger, Hollinger Inc. sought to enjoin a proposed sale by its direct subsidiary Hollinger International, Inc. of an indirect, wholly-owned subsidiary (the Telegraph Group Ltd. (England)) on the basis that the proposed sale constituted substantially all of the assets of Hollinger International and therefore Hollinger Inc. and the other stockholders of Hollinger International were entitled to vote on the sale under Title 8, Section 271 of the Delaware Code. Hollinger, 858 A.2d at 346; see 8*

Del. C.§ 271.

5. *In arguing against an injunction, Hollinger International contended the proposed sale did not trigger Hollinger Inc.'s rights under Section 271 because the Telegraph Group sale was not a sale of substantially all of Hollinger International's assets, but rather a sale of the assets of an indirect, wholly-owned subsidiary. Hollinger International asserted that the Telegraph Group was 'held through a chain of wholly owned subsidiaries' of Hollinger International and 'only the last link in that chain' was being sold. Hollinger, 858 A.2d at 347. Therefore, Hollinger International argued, Section 271 should not apply because it 'does not contemplate ignoring the separate existence of subsidiary corporations unless the stringent test for veil piercing is met.' Id. at 373.*

6. *In declining to grant an injunction, the court chose 'not to decide whether [Hollinger] International's technical statutory defense ha[d] merit' and instead 'treat[ed] the Telegraph Group as if it were directly owned by [Hollinger] International,' thereby setting aside the levels of corporate separateness in the "chain" for purposes if its analysis. Id. at 348. The court explained: 'It is common for public companies to hold all of their operating assets through indirect, wholly owned subsidiaries. [Hollinger] International wants me to hold that [as an intermediate] parent company [its] board may unilaterally direct and control a process by which its indirect, wholly owned subsidiary sells assets that would, if held directly by [Hollinger] International, possibly comprise substantially all of [its] assets and by which the sale proceeds under a contract that [Hollinger] International itself negotiates, signs, and fully guarantees. In that circumstance, [Hollinger] International says that § 271 would have no application unless the selling subsidiary has no corporate dignity under the strict test for veil piercing. A ruling of that kind would, as a practical matter, render § 271 an illusory check on unilateral board power at most public companies.*

7. *Importantly, the court discussed Hollinger International's argument that Section 271 'does not apply to a sale of an asset by a wholly owned subsidiary unless the subsidiary's existence would be disregarded under the standard for piercing the corporate veil.' Id. at 371; accord id. at 373, 375. The court found there was no basis for veil-piercing between Hollinger International and the lower subsidiaries in the chain. Id. at 348, 371, 374–75. The court explained that the chain of subsidiaries was 'formed because they had valuable tax, financial, and liability-insulating purposes' and Hollinger International had 'maintained the corporate formalities necessary . . . to comply with . . . regulatory requirements.' Id. at 372. Therefore, under the stringent veil-piercing test, the corporate separateness would be respected. But the court's analysis did not end there.*

8. *The court concluded it was 'clear' that Hollinger International 'directed and controlled' the dealings with respect to the Telegraph Group,[2] including directing and controlling the sale of the Telegraph Group through the chain of subsidiaries Hollinger International wholly owned and controlled, with each subsidiary in the chain following Hollinger Inc.'s directives with respect to the sale. Id. at 372–73. By its promise to dispose of the Telegraph Group and 'bear all the economic risks of the asset sale itself,' Hollinger International 'essentially eliminat[ed] the subsidiary's purpose and existence and monetiz[ed] for itself as parent the value of the assets held by that subsidiary.' Id. at 375.*

9. *Thus, notwithstanding that Hollinger International and its chain of subsidiaries, including the Telegraph Group, embodied the hallmarks of*

traditional corporate separateness and there was no basis for veil-piercing, the court decided the question of whether Hollinger Inc. and the other stockholders of Hollinger International were entitled to a vote on the sale under Section 271 without regard to corporate separateness, assuming for purposes of its analysis that the Telegraph Group –the last link in the 'chain' of indirect subsidiaries – was directly held by, and would be sold by, Hollinger International.

10. *In doing so, the court rejected the contention 'that a wholly owned subsidiary is either without any legal dignity at all in the sense that it fails the severe test required to pierce the corporate veil or else its separate existence must be recognized in all contexts.' Id. at 374–75. The court reasoned, this "stark, binary approach . . . does not comport with the approach Delaware has taken in other areas of its corporate law' and 'creates a Hobson's choice that seems unnecessary.' Id. at 375.[3] Ultimately, the court concluded that the qualitative and quantitative value of the challenged sale did not meet the threshold requirement of 'substantially all' of Hollinger International's assets necessary to require a stockholder vote under Section 271 and declined to grant an injunction on that basis.*

11. *The Hollinger case reinforces Justice Holland's conclusion that Section 271 has codified the principle of Delaware law that corporate formalities may be set aside in certain circumstances. Hollinger also demonstrates that the Delaware courts may apply and extend the principles of corporate separateness as a matter of practicality and equity. In Hollinger, the court chose to disregard corporate separateness for the specific purposes of its analysis under Section 271, while still finding no basis for veil-piercing – thereby rejecting any assertion that veil-piercing is the only instance in which corporate separateness may be disregarded.[4]*

12. *As shown in Hollinger, as well as in sections of the Delaware Code like Sections 220 and 271, Delaware law recognizes that a parent corporation has the legal and equitable right to exercise control over and direct its subsidiaries and their assets and that a subsidiary must acquiesce in that properly-exercised control. Applying those principles, the Golian Statement makes clear that BMS Co, as 100% owner of BMS Pharma, directed and controlled BMS Pharma's intellectual property assets and that BMS Pharma followed BMS Co's directives with respect to those assets. Accordingly, I reaffirm my agreement with Justice Holland's conclusion that BMS Co had the right to cause its wholly-owned subsidiary, BMS Pharma, to assign to BMS Co the right to claim priority from the first-filed patent application, as matter of its control over a wholly-owned subsidiary.*

The Digitech Case

13. *The Steele Report also disagrees with Justice Holland's opinion that a Delaware court would find BMS Co had equitable or beneficial title to BMS Pharma's patents because it was the ultimate decision maker for BMS Pharma, as demonstrated by BMS Co's established practice of resting legal ownership of certain intellectual property assets with its wholly-owned subsidiaries, including BMS Pharma, while retaining beneficial ownership of and its attendant control over those assets. I continue to agree with Justice Holland.*

14. *Chief Justice Steele contends that 'the mere possibility for a corporate parent to instruct a subsidiary to assign an asset does not, under the laws of Delaware, equate to an assignment actually carried out.' Steele Report ¶ 32 (referencing the proposition that federal patent law preempts state law with*

respect to property interests in patents). The Steele Report relies on Digitech Image Techs., LLC v. Newegg Inc., 2013 WL 1871513 (C.D. Cal. May 3, 2013), for the proposition that Delaware property law regarding equitable title is in conflict with federal patent law, because as a matter of federal patent law, BMS Co would have had no legal right to control or direct action with respect to BMS Pharma's patents in the absence of a formal legal assignment. See Steele Report ¶ 31.

15. *Chief Justice Steele's reliance on Digitech is misplaced for two reasons. First, it is my understanding that state law governs ownership and control of patent property rights, as the Thomas Report that Chief Justice Steele relies upon concedes. See Thomas Report § 25. As stated in the Irish Chisum Report (¶ 16), the U.S. Court of Appeals for the Federal Circuit – the primary forum for deciding issues of U.S. patent law – has concluded that 'the question of whether a patent is valid and infringed ordinarily is one for federal courts, while the question of who owns the patent rights…is a question exclusively for state courts,' and has noted 'that long has been the law.' Schwendimann v. Arkwright Advanced Coating, 959 F.3d 1065, 1072 (Fed. Cir. 2020) (quoting Jim Arnold Corp. v. Hydrotech Sys., Inc., 109 F.3d 1567, 1571 (Fed. Cir. 1997)); accord id. (stating that 'legal title to the patent or patent application…is determined by state law'); Enovsys LLC v. Nextel Commc'ns Inc., 614 F.3d 1333, 1342 (Fed. Cir. 2010) ('Who has legal title to a patent is a question of state law.' (collecting cases)). As Professor Chisum explains, 'a person or entity may have equitable rights to an invention or patent right even though there is no written assignment of legal title.' Irish Chisum Report ¶ 25. Thus, it is my understanding that federal law does not preempt the principles of equitable title set forth in the Holland Report and my Initial Statement, and the principles of Delaware law cited in our reports apply when determining whether BMS Co had ownership rights in the subject patents such that it could order their assignment.*

16. *Second, even if one was to assume federal law applies, there is no 'conflict' between Delaware's principles of equitable title and federal law. In Digitech, a federal court considered whether an entity had standing to bring a patent infringement action. Digitech, 2013 WL 1871513, at *3. The court explained that '[p]atent rights are not acquired unless authorized by, and acquired in, the manner prescribed by statute,' id. at *5, and 'a parent company generally cannot sue for patent infringement on behalf of its patent-holding subsidiary' in an action at law seeking money damages. Id. at *3. Nonetheless, the court acknowledged, '[t]here is also authority that recognizes standing for equitable-title holders to a patent.' Id.*

17. *Consistent with the Holland Report, Digitech explains that '[e]quitable title may be defined as the beneficial interest of one person whom equity regards as the real owner, although the legal title is vested in another.' Id. (internal quotation marks omitted).[5] But 'the mere fact that a corporation's subsidiary owns a patent is insufficient to establish that the corporation has equitable title to the patent." Id. at *4. Because there was no written assignment to give the parent company standing to seek legal remedies and because the only allegation proffered in support of equitable standing was the parent's mere ownership of the subsidiary, the Digitech court dismissed the action for lack of standing.*

18. *Here, however, BMS Co has established that its relationship with BMS Pharma goes beyond mere stock ownership. As set forth in the Golian Statement, BMS Co had and continues to have complete control over BMS Pharma and the patents in question. Both BMS Co and BMS Pharma had a policy of ensuring BMS Co made all decisions with respect to those patents,*

notwithstanding that BMS Pharma retained legal title. Indeed, the decisions regarding BMS Pharma's patents are made by BMS Co's intellectual property lawyers, often in consultation with BMS Co's tax department and other areas of BMS Co's legal department, as BMS Pharma does not have its own independent intellectual property lawyers or legal department.

19. *With these facts in mind, Hologic, Inc. v. Minerva Surgical, Inc., 163 F. Supp. 3d 118 (D. Del. 2016), is instructive. In Hologic, the court echoed the general principles articulated in Digitech, but went on to conclude that a parent company had equitable standing with respect to its subsidiary's patents. Id. at 122. The court explained the 'mere fact' of stock ownership or of a corporate relationship does not establish standing, but the record in that case demonstrated 'that boundaries between the corporations at bar ha[d] been breached' such that the parent had equitable title to the patents and, accordingly, equitable standing. Id.*[6]

20. *The record in Hologic reflected that the subsidiary owned the patents-in-suit and the parent owned and 'exercised . . . complete control over [the subsidiary],' including over the subsidiary's business decisions and patent enforcement, assignment, and licensing policies. Id. According to the parent, '[b]ecause of the structure of this corporate relationship and [parent's] complete control over [the subsidiary's] patent licensing and enforcement policies, [parent] has had control over the Patents-in-Suit, and has enjoyed exclusive rights thereunder.' Id. Under these circumstances, the court held, the parent 'has established its equitable standing to pursue injunctive relief.' Id. (citing Cognex Corp. v. Microscan Sys., Inc., 2014 WL 2989975, at *5 (S.D.N.Y. June 30, 2014), Atmel Corp. v. Authentec, Inc., 490 F. Supp. 2d 1052, 1055 (N.D. Cal. 2007), and Pipe Liners, Inc., 893 F. Supp. at 706).*

21. *Similarly here, and consistent with Justice Holland's conclusion, notwithstanding the absence of a formal assignment, the relationship and practices between BMS Co and BMS Pharma demonstrate that BMS Co retained equitable title, and therefore control, over BMS Pharma's patents, including the power to direct and assign those patents. Therefore, BMS Co had and has the absolute right to direct the legal title holder of the patent, BMS Pharma, to take any and all action regarding the patent that is in the best interest of BMS Co.*

Conclusion

22. *For the reasons explained above, I reaffirm my agreement with the Holland Report.*

[Footnotes]

[1] *Capitalized terms not defined in this statement have the same definition as in my Initial Statement.*

[2] *The court explained that Hollinger International's 'wholly owned subsidiaries did what wholly owned subsidiaries do – the bidding of their sole owner.' Hollinger, 858 A.2d at 372– 73; see also Trenwick Am. Litig. Tr. v. Ernst & Young. L.L.P., 906 A.2d 168, 173 (Del. Ch. 2006) ('Wholly-owned subsidiary corporations are expected to operate for the benefit of their parent corporations; that is why they are created.').*

[3] *See Sternberg v. O'Neil, 550 A.2d 1105, 1125 n.45 (Del. 1988) (noting the possibility of holding a parent subject to jurisdiction in Delaware based on its instigation of the subsidiary's acts in the state); Weinberger v. UOP, Inc.,*

*457 A.2d 701 (Del. 1983) (demonstrating that when a controlling stockholder directly controls the affairs of a publicly held subsidiary through its representatives on the subsidiary's board, the parent is subject to direct liability for breach of fiduciary duty); see also Metro Storage Int'l LLC v. Harron, 2019 WL 3282613, at *25 (Del. Ch. July 19, 2019) (rejecting argument that an 'agency' or 'fiduciary' shield protected LLC manager from liability and approvingly citing Hollinger); Leslie v. Telephonics Office Techs., Inc., 1993 WL 547188, at *8–9 (Del. Ch. Dec. 30, 1993) (noting the possibility that a parent-level vote would be required if the court were to conclude that the subsidiary corporation had functioned merely as the instrumentality or agent of the parent in effecting the asset sale).*

4 *Indeed, veil piercing is a harsh and narrowly applied result that would allow a plaintiff to reach through the assets of a subsidiary to collect from a parent where a parent has ignored corporate formalities and abused the purposes of corporate separateness. E.g., Verdantus Advisors, LLC v. Parker Infrastructure P'rs, LLC, 2022 WL 611274, at *2 (Del. Ch. Mar. 2, 2022) (stating that "[v]eil piercing is a tough thing to plead and a tougher thing to get," and that Delaware courts have "required a veil-piercing claim to demonstrate an overall element of injustice or unfairness" (internal quotation marks omitted)); Doberstein v. G-P Indus., Inc., 2015 WL 6606484, at *4 (Del. Ch. Oct. 30, 2015) ('The case law governing veil-piercing requires me to consider whether the individual defendant…abused the corporate form and, through that abuse, perpetrated fraud on an innocent third party.'); In re Sunstates Corp. S'holder Litig., 788 A.2d 530, 534 (Del. Ch. 2001) (noting that "to pierce the corporate veil based on an agency or 'alter ego' theory, the corporation must be a sham and exist for no other purpose than as a vehicle for fraud' (internal quotation marks omitted)).*

5 *See also Pipe Liners, Inc. v. Am. Pipe & Plastics, Inc., 893 F. Supp. 704, 706 (S.D. Tex. 1995) (defining equitable title as 'the beneficial interest of one person whom equity regards as the real owner, although the legal title is vested in another"); Arachnid, Inc. v. Merit Indus., Inc., 939 F.2d 1574, 1578–80 & n3. (Fed. Cir. 1991) (discussing possibility of a court having jurisdiction over claims for equitable relief by an equitable title holder of a patent, and defining equitable title as 'the beneficial interest of one person whom equity regards as the real owner, although the legal title is vested in another').*

6 *Quoting Top Victory Elecs. v. Hitachi Ltd., 2010 WL 4722482, at *3 (N.D. Cal. Nov. 15, 2010) ('While the Federal Circuit has been clear that ownership, assignment, or an exclusive license are required for legal remedies, it has indicated that in some circumstances an equitable owner without legal title may pursue equitable remedies. This Court has held that even if the companies are closely operated and the parent purports to act on behalf of the subsidiary, a parent does not have standing in a suit involving patents held by a subsidiary without a showing that boundaries between the corporations have been breached.' (citations omitted))."*

APPENDIX 2

Abridged Written Evidence of Professor Chisum

"*14. ...Professor Thomas correctly states that state law, not federal patent law, governs ownership of property, including 'intellectual property,' and the interpretation of contracts. However, he incorrectly states at paragraph 31 that 'federal law governs the way in which an assignment of patent right (including the right to claim priority) can be made.' For that reason, Professor Thomas errs in dismissing the expert opinion by the late Justice Randy J. Holland (and now of Chancellor Chandler) that Delaware state law established a beneficial, i.e., equitable, ownership of a patent application and a right to claim priority from that patent application. All the cases Professor Thomas cites and discusses, including ones on the separateness of corporations, pertain to a 'federal' issue, to wit, 'standing' to sue for infringement of an issued patent in federal court and, specifically, whether there has been an assignment in writing as required as a matter of federal law for that purpose. None pertained to ownership of an application or of a right to claim priority for any other purpose. None rejected, based on federal law, any state law-based ownership of an application or right to claim priority. Standing is specifically governed by the federal patent statutes. The statutes recite that a 'patentee. can sue for infringement, i.e., has '*remedy by civil action for infringement of his patent*' (35 U.S.C. § 281). The statutes also provide, in effect, that one can become such a patentee by an assignment in writing (35 U.S.C. § 261). That requirement for standing exists alongside the separate question of ownership of patent rights, which is governed by state law. As I explain below, even in regard to standing, federal courts apply state law to ownership and contract issues with only a narrow exception (to wit, whether a contract to transfer a patent right is a present assignment or an agreement to assign in the future). The matter here does not involve standing and is not within that exception.*

15. As also explained more fully below, nothing in Professor Thomas's comments on my Italian statement [a statement delivered by Prof. Chisum in the Italian limb of these proceedings] *undermines the above conclusion. To support his reliance on Federal Court standing decisions, Professor Thomas postulates that there is or should be, for 'policy' reasons, a 'uniform' approach to 'corporate structure' applicable to all patent law issues, including equitable ownership of patent priority rights. Further, he indicates, in effect, that the rule should be that for standing to sue for infringement of a patent in federal court, to wit, a written assignment of legal title of a particular patent or application as per 35 U.S.C. § 261. Whether or not desirable as policy matter, that approach does not reflect current established law. Case authority, including that of the Supreme Court, confirms that compliance with the statute on assignment of legal title (Section 261) does not apply to equitable ownership, which can be transferred via specifically-enforceable legal obligations. That there is no 'uniform' rule on ownership of patent rights follows from the principle that, as Professor Thomas states, 'state law governs the ownership of property.' The laws of particular states can vary. Thus, the law of the state of Delaware on equitable ownership between related corporations, as described in the late Justice Holland's report (and as per the Chandler Statement), may vary from that of another state, such as Texas, California or New York. Importantly, under the United States constitution, there is no general federal law common law. Thus, there is no*

basis for extending for policy reasons the federal statute on assignments of patents to cover all aspects of ownership.

16. *Professor Thomas' concession in paragraph 30 of the Thomas Statement that state law generally governs ownership of patent rights is supported both historically and by recent case authority. For example, in* Schwendimann *v.* Arkwright Advanced Coating*, 959 F.3d 1065 (Fed. Cir. 2020), which was a standing case, the Federal Circuit quoted a 1997 decision, which stated: 'It may seem strange at first blush that the question of whether a patent is valid and infringed ordinarily is one for federal courts, while the question of who owns the patent rights ... is a question exclusively for state courts. Yet that long has been the law.' 959 F.3d at 1072 (quoting* Jim Arnold Corp. *v.* Hydrotech Sys., Inc.*, 109 F.3d 1567, 1571 (Fed. Cir. 1997)).* Schwendimann *also demonstrates that compliance with Section 261 and ownership of the right in question are separate requirements that must be met for the purpose of standing:*

> *'In addition to the § 261 written instrument requirement of assignment, the plaintiff must have the legal title to the patent or patent application, which is determined by state law. See* Enovsys LLC *v.* Nextel Commc'ns Inc., *614 F.3d 1333, 1342 (Fed. Cir. 2010)'*
>
> *NOTE: In his 'Comment' at paragraph 65 of Professor Thomas suggests that my citation of Schwendimann is a recognition that 'this line of cases,' i.e., standing cases, is 'highly pertinent to the present matter.' To the contrary, I cited Schwendimann for its acknowledgment that federal law, including standing, does not control ownership, which is a matter of state law.*

17. *Because standing was at issue in* Schwendimann*, the Federal Circuit appropriately focused on whether there was a writing that transferred legal title and held, based on state law, that there was. It did not address equitable title.*

18. *Professor Thomas and I rely primarily on decisions by the Court of Appeals for the Federal Circuit because it has exclusive jurisdiction over appeals from both district courts and the U.S. Patent and Trademark Office in patent cases. Thus, its precedents dominate issues of U.S. patent law except on issues that the U.S. Supreme Court has addressed. As noted in the next paragraph, the question whether an assignment of an equitable interest in a patent right requires an express written agreement is one upon which the Supreme Court has spoken. Also, the Federal Circuit may be required in particular cases to address issues of state law, but its opinions cannot be authoritative on those issues. The courts of a given state determine what that state's law is.*

19. *There is no requirement that a specific written assignment is necessary to convey equitable title to an invention, a patent application, or a right to claim priority based on a patent application. Over a century ago, the United States Supreme Court stated: 'An oral agreement for the sale and assignment of the right to obtain a patent for an invention is not within the statute of frauds, nor within [the statute] requiring assignments of patents to be in writing; and may be specifically enforced in equity, upon sufficient proof thereof.'* Dalzell *v.* Dueber Watch-Case Mfg. Co.*, 149 U.S. 315, 320 (1893).*

20. *The 'statute' requiring assignments 'to be in writing' the Supreme Court referred to in* Dalzell*, Revised Statute Section 4898, was the predecessor to the current assignment statute (35 U.S.C. § 261). Thus, the Court's holding in* Dalzell *establishes that a written assignment of a patent right is not necessary for a conveyance of equitable title. Consistent with Dalzell, Section 261 has never been applied in a case involving a dispute over*

ownership of a patent priority right (as opposed to ownership for purposes of standing to sue for infringement of a patent).

21. *The right of specific enforcement in 'equity', the Court referred to in* Dalzell*, is the basis for recognizing an immediate 'equitable title' in a person or entity who has, because of some obligation, a right to demand an order transferring legal title to a patent application, a right to claim priority, or a patent. As noted in* Arachnid, Inc. *v.* Merit Industries, Inc., *939 F.2d 1574 (Fed. Cir. 1991), 'equitable title' 'may be defined as 'the beneficial interest of one person whom equity regards as the real owner, although the legal title is vested in another.'* Black's Law Dictionary *1486 (6th ed. 1990).' 939 F.2d at 1578 n.3.*

22. *That the assignment statute (Section 261) does not apply to transfers of an equitable interest is confirmed by the statute's language. It states that applications and patents are 'assignable in law.' The reference to 'law' links to the fundamental distinction in United States jurisprudence between law (or 'common law') and equity.*

23. *State courts have applied Dalzell and the concept of equitable title to questions of patent right ownership in the context of corporate separateness as well as in that of employed inventors. E.g.,* Dickman *v.* Vollmer*, 303 Wis. 2d 241, 736 N.W.2d 202 (Wis. Ct. App. 2007).*

24. *NOTE: In paragraph 66, Professor Thomas criticizes my reliance on* Dalzell*, characterizing that decision, as a 'nineteenth century opinion' that involved 'entire dissimilar facts to the present matter' and having 'nothing to teach us about the relevance of Delaware corporate law to the facts at hand.' However,* Dalzell *is a decision by the United States Supreme Court. It is binding unless and until the Court overrules it or it is superseded by statute. As explained above,* Dalzell *specifically held that the patent statute requiring a written assignment (Section 261) does not apply to specifically enforceable obligations to assign patent rights, i.e., to the transfer of equitable title. Thus, it is highly relevant to the issue at hand and undermines Professor Thomas' proposal that a written assignment was required for a recognition of transfer of equitable title from one corporate entity to a related corporate entity. Dalzell is not a forgotten relic of the past. Cases such as Dickman cite Dalzell as authority for ordering specific performance of an agreement to assign a patent right and for the inapplicability of the Section 261 written assignment requirement. Another example is* SourceProse Corp. *v.* RPX Corp.*, 2017 WL 373065, *6-*8 (N.D. Calif. 2017).*

25. *The principle that a person or entity may have equitable rights to an invention or patent right even though there is no written assignment of legal title has long been recognized in the rules on filing an application when an inventor refuses to cooperate with an owner of rights in an invention. Prior to the 2011 America Invents Act (AIA), Section 118 of the Patent Act provided that:*

> *'Whenever an inventor refuses to execute an application for a patent, or cannot be found or reached after diligent effort, a person to whom the inventor has assigned or agreed in writing to assign the invention or who otherwise shows sufficient proprietary interest in the matter justifying such action, may make application for patent on behalf of and as agent for the inventor on proof of the pertinent facts and a showing that such action is necessary to preserve the rights of the parties or to prevent irreparable damage; and the Director may grant a patent to such inventor upon such notice to him as the Director deems sufficient, and on compliance with such regulations as*

he prescribes.' 35 U.S.C. Section 118 (before revision) (Emphasis added.)

26. *Thus it authorized filing by a person 'to whom the inventor has' assigned an invention or who 'shows sufficient proprietary interest in the matter' even though there is no assignment or agreement to assign 'in writing.' This principle has been retained by the AIA and as amended section 118 authorizes applications as follows:*

> *'A person to whom the inventor has assigned or is under an obligation to assign the invention may make an application for patent. A person who otherwise shows sufficient proprietary interest in the matter may make an application for patent on behalf of and as agent for the inventor on proof of the pertinent facts and a showing that such action is appropriate to preserve the rights of the parties.' 35 U.S.C. Section 118 (revised) (Emphasis added.)*

NOTE: In paragraphs 55 to 57 of the Thomas Statement, Professor Thomas indicates that Section 118 was 'a narrowly drawn provision that speaks to circumstances not relevant to the present matter.' However, as I note above, Section 118, in both its earlier and its later form, represent a recognition in the federal patent statutes of the established general principle that there can be a 'proprietary' interest, i.e., ownership, in an invention and patent priority rights beyond those already perfected by a written assignment complying with the federal statutes (i.e., Section 261).

27. *Starting at Paragraph 31 of the Thomas Statement, Professor Thomas asserts that 'federal law governs the way in which an assignment of patent rights (including the right to claim priority) can be made.' That is incorrect. Federal law only governs assignments of patent rights to the extent that Section 261 imposes an in writing requirement that applies to assignments of legal title in certain circumstances, such as for the purpose of standing, but is not otherwise relevant to assignment or transfer of ownership in patent rights, including equitable title, which are matters of state law.*

28. *At Paragraph 32 of the Thomas Statement, the* Stanford *case is cited as the 'leading case in this area' and quoted. However, the quotation itself shows that federal law is an 'exception' and limited to a specific question: 'whether contractual language effects a present assignment of patent rights, or an agreement to assign rights in the future.'*

29. *The Stanford case itself vividly illustrates the difference between standing and ownership and the respective roles of federal and state law. The plaintiff lacked standing under federal law to sue a company for infringement of a patent because a named co-inventor had earlier assigned his legal title to the sued company. Yet the sued company was barred from obtaining ownership of the patent from the plaintiff by virtue of state law rules.*

30. *Paragraph 33 of the Thomas Statement states that state law and federal law must be 'considered together in order to determine whether a particular purported transfer of patent rights is valid.' That is true in the context of standing to sue for infringement. It is not true in all contexts. Paragraph 34 repeats the 'combined effect' assertion.*

31. *Paragraph 35 of the Thomas Statement states, correctly, that Delaware law 'would govern the interpretation of particular contractual elements of an assignment.' Professor Thomas then notes that the following 'analysis ... focuses on the federal laws that govern an assignment of patent rights.' The*

analysis consists of cases addressing the requirement that an assignment be in writing for the purposes of standing to sue in federal court for infringement. None of the cited cases addressed requirements for the assignment of patent rights in any other context or for ownership generally, which is a matter of state law.

32. *Paragraph 36 of the Thomas Statement describes and quotes Section 261, on the requirement of an 'instrument in writing' for an assignment, as governing 'the transfer of patent rights.' However, as noted above, the Supreme Court in 1893 held that the statute did not apply to equitable title. Thus, the statute governs assignments of legal title to patents for determining status as a 'patentee' for the purpose of standing to sue for infringement.*

33. *At paragraph 37 of the Thomas Statement, Professor Thomas cites a District Court decision,* Software Rights Archive, LLC *v.* Google Inc.*, 2009 U.S. Dist. LEXIS 26640, 2009 WL 901361 (E.D. Tex. 2009), as stating that 'the statute' (i.e., Section 261) 'imposes minimal requirements' for an assignment. The issue in* Software *was standing to sue. Nevertheless, it is of interest that* Software *went on to stress that '*[w]hen determining ownership of a patent in the context of a contract or agreement, state law governs.*' Importantly, it also applied Delaware state law on corporate separateness and disregarded a 'corporate distinction' between two entities for the purpose of 'vesting title' in a plaintiff.*

34. *Paragraph 38 of the Thomas Statement discusses a district court case,* Schwendimann*, on the meaning of 'instrument in writing.' It is a standing case and therefore the Section 261 '*writing requirement*' applied to the assignment in question. It emphasized that '*even without a signature*,' a '*document could still be a written instrument under federal law.*' It also noted that 'ownership' was 'determined by state law.'*

35. *Paragraph 39 of the Thomas Statement indicated that, in the present matter, there was 'no purported tangible form of an assignment' except for an email chain. No authority is cited on why an email chain was not a writing or why a 'right to call' for an assignment must have been exercised in order to recognize equitable title. NOTE: In paragraph 68, Professor Thomas suggests that I was asserting an 'alternative argument,' to wit, that the email chain was 'a written assignment.' In fact, I stated only that Professor Thomas did not cite authority on why an email could not be a writing nor why an email chain could not be a basis for an assignment of equitable title. In paragraph 69 of the Thomas Statement, Professor Thomas agrees that an 'email chain could constitute an instrument in writing'. He then critiques a witness statement's description of the email chain at issue in the present case. The proper interpretation of the email chain, in particular, whether it evidences or creates a specifically enforceable obligation to transfer patent rights, would be under Delaware state law, not federal patent law.*

36. *Beginning with paragraph 40 of the Thomas Statement, Professor Thomas reviews and criticizes the report of late Justice Holland. The primary criticism is, in effect, that Justice Holland failed to consider federal court opinions on patents and, in particular opinions, indicating a 'prevailing view that a parent corporation possesses neither legal nor equitable title in patents that are owned by the subsidiary.' However, all the cited opinions are in the context of applying the federal law on standing to sue for infringement of a patent. None concerned state law on ownership of equitable title to patent rights. None indicated that federal law overrode a specific rule of state law. Therefore, because the ownership question at issue (that is, of succession to title to a patent application and priority right), was a matter of Delaware state law, not federal patent law, the failure to consider federal court patent cases was not a flaw in Justice Holland's report (just as it is not a flaw in the*

Chancellor Statement).

37. *Paragraphs 41-44 of the Thomas Statement discuss the Federal Circuit's 2010 Spine Solutions decision. That decision noted that the only question in that case was whether a party was 'an exclusive licensee for purposes of standing.' The decision does not cite, discuss or repudiate any issue of state law. In passages Professor Thomas quotes, Spine noted that it was 'undisputed' that one entity was the 'sole owner,' that there was 'no agreement, either oral or written' with respect to a patent. The party asserted, at most, that there was an 'understanding' with the patent owner that it would have an exclusive right to practice the patent. That 'understanding' was not asserted to be one of ownership. It was 'at most' a bare license. Thus, Spine did not consider or reject any theory of equitable title based on the facts and the applicable state law.*

38. *Paragraphs 45 and 46 of the Thomas Statement discussed the Federal Circuit's 2010* Abraxis *decision. However, it too was a standing case concerning legal title. It indicated that, within a 'common corporate structure,' an 'appropriate written assignment' was 'necessary to transfer legal title' without which a party 'had no standing to bring this infringement action.' 620 F.3d at 1318.*

39. *At the end of paragraph 46 of the Thomas Statement, Professor Thomas concedes that* Abraxis *spoke only of 'legal title' but argues that its reasoning and ruling extended to finding that the party also lacked 'equitable title.' That was because the remedy the party sought was 'equitable', an injunction against future infringement. However, any such hypothetical holding would still be a matter of federal court standing and not binding against an otherwise proper showing of ownership under state law for other purposes. Regardless, the* Abraxis *case's holding was, explicitly, that the absence of a written assignment of legal title precluded standing. It rejected an argument, based on* Arachnid, Inc. *v.* Merit Indus.*, 939 F.2d 1574 (Fed. Cir. 1991), that 'equitable title to the asserted patents' was 'sufficient to confer standing.'* Abraxis *distinguished Arachnid as involving a specific exception: 'a present agreement to assign rights to future inventions.' That exception did not apply in* Abraxis. *Neither* Abraxis *nor* Arachnid *indicated that federal law required a written assignment for a transfer of equitable title or that federal law preempted state law on ownership of patent rights.*

40. *There is no basis for considering* [the] *Abraxis decision to be a 'leading one' as paragraph 45 of the Thomas Statement suggests. Indeed, in a recent decision, in* Schwendimann *v.* Arkwright Advanced Coating*, 959 F.3d 1065 (Fed. Cir. 2020), the Federal Circuit held that a reformation of an agreement under state law could retroactively cure a 'standing' issue. It distinguished* Abraxis. *959 F.3d at 1047 n6. NOTE: In paragraph 67, Professor Thomas contests whether* Abraxis *is a 'leading' case, indicating that it had been cited 975 times. I sampled a few decisions citing* Abraxis. *They cited* Abraxis *for various general propositions on the law of standing. Professor Thomas did not identify any case citing* Abraxis *as a leading decision on the specific proposition that a written assignment was necessary for a corporation to have equitable title to a patent right the legal title to which was in a related corporation.*

41. *Paragraphs 47 through 50 of the Thomas Statement discuss district court decisions. All are in the context of federal court standing.*

42. *Digitech, discussed in paragraphs 47 and 48 of the Thomas Statement, concerned standing. It indicated that, under the facts, there was no basis for disregarding corporate separateness and therefore finding equitable title in a parent corporation under either state corporation law or patent law. It did not consider whether additional facts might establish equitable title in a related*

corporation under the applicable state law.

43. *In Paragraphs 52 to 69, Professor Thomas offered comments on my Italian statement.*

44. *In Paragraphs 55 to 57, Professor Thomas addresses the 'Role of Section 118 of the U.S. Patent Act.' As I note in paragraphs 25 and 26 above, Section 118 is statutory recognition that persons can have ownership of inventions and patent filing and priority rights beyond those perfected by Section 261 written assignments. The primary source of those rights is state law or even the law of another country. An example is* Akazawa *v.* Link New Technology International, Inc., *520 F.3d 1354, 1355 (Fed. Cir. 2008) (Japanese intestacy law).*

45. *In paragraphs 58 to 64 of the Thomas Statement, Professor Thomas addressed 'The Role of Standing.'*

46. *In paragraph 58 of the Thomas Statement, Professor Thomas asserts that I 'summarily' dismiss a 'long list of opinions 'holding that corporate parents do not hold equitable title in patents owned by their subsidiaries' because they 'primarily pertained to standing.' To the contrary, I carefully considered each case Professor Thomas cited and determined that they not only pertained to standing but also did not apply federal standing law to override a showing that a corporate entity had equitable title under state law. The decisions held that a corporate entity lacked standing because it did not possess legal title via a Section 261 assignment in writing. Some, such as* Beam Laser *(2000), and* Steelcase *(2004), ruled that a parent corporation failed to establish that it had 'equitable title' to patents to which a subsidiary held legal title such as would support standing to seek equitable remedies. In Beam Laser, the district court did not cite or consider any asserted provision of state law supporting such title. Had the parent done so, the district court would have been bound to apply that law, as the Federal Circuit confirmed in* Schwendimann *v.* Arkwright Advanced Coating, *959 F.3d 1065 (Fed. Cir. 2020), discussed above. In Steelcase, the district court carefully considered the facts and found standing for one subsidiary but not another.*

47. *In paragraph 58 of the Thomas Statement, Professor Thomas also asserts (without citation of authority): 'Simply because a principle of law is frequently articulated within one context does not suggest that it does not apply equally in a related context.' In my opinion, the opposite is true in this instance. The rule requiring a written assignment is, indeed, 'frequently articulated' in the context of standing to sue for infringement. That is because about 4000 patent suits per year are filed in the district courts. A standing issue arises in a significant number of them. As a result, there are many, easily accessible case precedents on standing, including by the Federal Circuit. Thus, Professor Thomas and I readily located and cited such cases. And it is certainly possible that some state courts might look to some standing rules. However, they are not compelled to do so. In contrast, the issue of ownership of applications and priority rights rarely results in litigation. It is tempting but erroneous to assume that the rules on standing apply to all other ownership contexts merely because they are frequently articulated.*

48. *In paragraph 59 of the Thomas Statement, Professor Thomas asserts that ownership is one or several components of standing and that it is wrong to 'dismiss' a standing case discussing ownership. This is true only to the extent that one considers carefully what a given standing case says and holds about ownership and in particular whether it addresses ownership, including equitable title, under the applicable state law (in this instance Delaware). One decision Professor Thomas cites,* Software Rights Archive, LLC *v.*

Google Inc.*, 2009 U.S. Dist. LEXIS 26640 *; 2009 WL 901361 (E.D. Tex. 2009), applied precisely that approach.*

49. *In paragraph 60 of the Thomas Statement, Professor Thomas asserts that I mistakenly stated, in paragraph 16 of my Italian statement, that Section 261 'is limited to determining whether a `patentee' has standing to sue for patent infringement.' However, paragraph 16 of my Italian statement states only: 'the statute governs transfer of patents for determining status as a 'patentee' for purpose of standing to sue for infringement.' It certainly does that. Section 261 links to Section 281, which states: 'A patentee shall have remedy by civil action for infringement of his patent.' Section 261 does also refer to 'applications,' and paragraph 16 of my Italian statement did not mean to state otherwise. For clarity, the pertinent sentence in Section 261 states: 'Applications for patent, patents, or any interest therein, shall be assignable in law by an instrument in writing.' NOTE: The reference to assignable 'in law' reinforces the case law discussed above holding the Section 261 assignment-in-writing provision does not apply to the vesting of beneficial title 'in equity.' See paragraph 22 above.*

50. *In paragraph 61 of the Thomas Statement, Professor Thomas asserts that 'US courts respect the formal differences between members of the same corporate family across the gamut of patent law issues.' He then discusses three such issues: remedies (paragraph 61), 'enforceability' (paragraph 62), and 'liability for patent infringement' (paragraph 63). All these issues are governed by federal patent law. Then, in paragraph 64 of the Thomas Statement, Professor Thomas argues, on policy grounds, that it makes no sense to have ownership 'depend upon which doctrine is being applied' or to have one person an owner of an invention or patent right 'with respect to one legal issue' but another owning it for another issue. The problem with this line of argument is that ignores the fundamental distinction between issues governed by federal law, including patent law, and those governed by state law, including equitable ownership of property. It is impermissible to ignore the fundamental divide between state and federal law for convenience or simplicity.*

51. *In paragraph 65 of the Thomas Statement, Professor Thomas approves of my citation of the recent Federal Circuit decision,* Schwendimann *v.* Arkwright Advanced Coating*, 959 F.3d 1065 (Fed. Cir. 2020). As I noted in paragraph 16 above, that case is pertinent to this matter not because it makes standing to sue rules 'pertinent to the present matter' but because it reemphasizes the importance of using applicable state law in determining ownership of patent rights.*

52. *In paragraphs 66 and 67 of the Thomas Statement, Professor Thomas criticizes my citations to* Dalzell *and* Abraxis*. I respond to those critiques in paragraphs 24 and 40 above.*

53. *In paragraph 68 and 69 of the Thomas Statement, Professor Thomas discusses the use of the email chain as evidence of an assignment. I comment on that use in paragraph 35 above.*

54. *In paragraph 70, Professor Thomas volunteered 'additional observations.'*

55. *First, in paragraph 71, he suggests that allowing assertion of possession of equitable title would have adverse consequences that would 'conflict with the policy goals of making ownership of patent rights orderly and predictable.' He cites no case authority that specifically subscribes to those general goals.*

56. *Second, in paragraph 72, he disagrees on policy grounds with the late Justice Holland's view about ownership issues being technical. No doubt there would be greater certainty if the law required all transfers of ownership rights of any kind to be in writing and recorded with the PTO. But that is not*

the current law. Also, it is not clear how knowing which enterprise possesses title to an invention would allow 'the USPTO to set clear boundaries on who may acquire and assert' as Professor Thomas asserts. Historically, and by longstanding practice, the PTO examines for the patentability of inventions and proper inventorship. It does not resolve disputes about ownership. See Chisum on Patents § 11.02[2][a][ii].

57. *In paragraph 73, Professor Thomas states his conclusion. Depending on how it is interpreted, his final statement is either tautological or untrue. He states: 'In the absence of a written assignment, US courts have refused to allow companies related to the patent owner to claim either a legal or equitable interest in that patent because the companies are commonly owned.' If 'patent owner' means an entity with full legal and equitable title, then, by definition, no other entity has a legal or equitable interest. And, in particular cases, courts have held that there was no showing of an equitable interest in a commonly owned corporation. But, in other cases, including one Professor Thomas cites, courts have found that there was an equitable interest. Thus, the courts have not always refused to allow a company related to the holder of legal title to a patent to claim an equitable interest.*

58. *In conclusion, it clear that, under United States law, ownership of a patent application and of a right to claim priority is governed by state law and not federal law. The federal statute referring to assignments 'in law' by an assignment in writing does not apply to equitable ownership of a right claim to priority. Therefore, in this case, state law applies. As described by both Chancellor Chandler and the late Justice Holland, under the state law of Delaware (which I understand is the applicable state law), the applicant for the 2002 PCT application was the beneficial owner of, i.e., holder of equitable title to, the right to claim priority stemming from the 2001 application and therefore, was a successor in title to that right*."

APPENDIX 3

Abridged Written Evidence of Dr Edwards

Statement #1 of 2

"[1] *….Skilled Person/Skilled Team*

5.1 *The concept of the 'skilled person or team' has been explained to me by Teva's solicitors, Pinsent Masons (Ireland), as a hypothetical construct which has been developed to help the court read, and understand patents essentially from the point of view of a person with an interest in reading the patent at the time it was written. My understanding of the concept of the skilled person, or by extension the skilled team, as explained to me is that the individual is a person skilled in the art to whom a patent is addressed and who would have a practical interest in the subject matter of the patent. The skilled person (which can be a skilled team) is uninventive but has the common general knowledge in the relevant field.*

5.2 *A skilled team (of people) would be a multidisciplinary team of subject-area experts working in the same company who are all working on the same project. Each, in their own subject area, has the interest, knowledge and access to general knowledge given above for the skilled person. The people may be drawn from scientific disciplines such as medicinal chemistry (those designing, synthesising the intended compounds and interpreting biological and other generated data in the design of the next round of compounds to be prepared), synthetic chemistry (those devising and executing synthetic routes to make the compounds), biologists (those designing the relevant biological assays and testing compounds produced, interpreting results) and pharmacologists, who are concerned with the action of a drug, which itself exerts a biochemical or physiological effect on the cell, tissue, organ or organism. There would also be drug discovery support specialists such as those undertaking experimental work and interpreting results for pharmacokinetic measurements, pharmacodynamics measurements, physiochemical assays such as solubility, lipophilicity and other relevant assays such as Cytochrome P450 assays, metabolism, etc. As well, specialists expert in high throughput screening (one source of chemical start points for the project; here there would be biologists and specialist technicians to use automation to deliver biological results on hundreds of thousands or millions of compounds). At the earlier stages of the project, clinicians would be involved in helping to define the requirements that the drug would need in order for it to be able to benefit patients.*

5.3 *I also understand that the relevant time for consideration is the Relevant Date.*

5.4 *Having looked at the patent applications set out at paragraph 3.3 above, I believe that the skilled team in 2001 are looking to discover inhibitors of trypsin-like serine protease, especially factor Xa. Further, I consider that W0652 is addressed to medicinal chemists ('Skilled Person' or 'skilled medicinal chemist') and pharmacologists (the 'Skilled Team'). I will focus on the skill set of a skilled medicinal chemist.*

5.5 *Typically the team member would possess a graduate or BSc/PhD degree in their chosen field, with a few years of experience working in industry. Interaction between team members would be via regularly scheduled team*

meetings where each discipline that has results produced over that reporting period would present these results and the team would discuss the opportunities arising, deciding on an appropriate course of action for the next reporting period. There would also be the opportunity for ad hoc meetings between Skilled Team members to discuss project results and progress.

5.6 The medicinal chemist is a generalist and would be expected to work on a number of different therapeutic indications and thus different projects over the course of their career, as I have done. A biologist tends to be more specialist and would, more often than not, work within one therapeutic area and indeed, often on a limited number of therapeutic target(s).

5.7 There are different stages at which the skilled medicinal chemist could be involved in a drug development project. The first is the Hit discovery stage, which is when the team is managing the output from a high throughput screen and using literature start points to initiate medicinal chemistry drug discovery efforts. The role of a medicinal chemist could continue through to Lead Optimisation ('LO') which is where the project has typically 1-2 series of compounds with associated data that marks out these series as worthy of further investigation. Typically the medicinal chemist would work on one project at a time.

5.8 There may, however, be opportunities for those working before LO (e.g., Hit discovery) to work on several projects simultaneously. Drug discovery support scientists would work on one or several projects concurrently.

5.9 A team may be composed, depending on the project stage, of around 5 to 30+ people.

5.10 I have worked on a number of different projects from Hit discovery through to LO. Examples of projects that I have worked on at Hit Discovery include oxytocin antagonists (inhibitors, worked on between approximately 1998 and 2001) and at LO would be NNRTi for HIV (worked on around 2001-2002). The next stage gate after LO is candidate drug delivery and I have worked on, for example, delivering OPP-IV inhibitors candidates (enzyme-class target, worked on approximately 2003-2005)....

[2] *Common General Knowledge*

6.1 I have been asked to describe the common general knowledge of the skilled medicinal chemist. It was common at the Relevant Date for a medicinal chemist to join a project in a therapeutic area with which they had no prior experience. This is because medicinal chemists typically work on numerous projects in different therapeutic areas over the course of their career, and apply their transferrable skills to a new setting.

6.2 Upon joining a new project, the medicinal chemists would typically perform a literature review and discuss with the biologists and pharmacologists to gain the relevant information. The sort of information of particular interest to the medicinal chemist is the target of interest (whether a molecule, enzyme, or receptor); the state of the art in terms of the types of molecules already known to interact with, and potentially inhibit, the target; and any structural based drug design efforts undertaken.

6.3 My understanding of the concept of common general knowledge, as explained to me, is that it represents the information that is generally known to the bulk of people working in a particular field and generally accepted by them as a reliable basis for further work at the relevant time. It encompasses material that the Skilled Person or Skilled Team can call to mind. It would therefore include the medicinal chemist's training, for instance, knowledge

of chemical reactions and their experience of how to develop potential drugs, for example by developing and considering SAR.

6.4 Furthermore, I understand that common general knowledge is typically represented by information in textbooks or published review articles (e.g., those in the Journal of Medicinal Chemistry), which were widely read or consulted at the relevant time and is not limited to the material that the Skilled Person or Skilled Team has memorised but also includes some information which is known to exist by the Skilled Person or Skilled Team and would be referred to by them as a matter of course ('CGK'). In terms of drug development, for example, the information would be that which is generally accepted by the bulk of people as a reliable basis for determining if a project should or should not continue to move forward through the stages of drug development.

[3] *Enzymes and Proteases*

6.5 An enzyme is a biological catalyst. It speeds up the rate of a specific chemical reaction in the cell. The enzyme is not destroyed during the reaction and is used over and over. A cell contains thousands of different types of enzyme molecules, each specific to a particular chemical reaction.

6.6 Enzymes in the human body are almost always proteins. Proteins are large molecules which are formed by the concatenation of amino acids. A protein may be described by the sequence of its constituent amino acids. In its physiological state, a protein "folds" into a three- dimensional structure. When folded, an enzyme then has an active site: this is the region of the molecule to which the natural substrate binds, being the molecule which the enzyme acts upon. The active site is crucial for the enzyme's catalytic activity.

6.7 A substrate is a molecule acted upon by an enzyme. A substrate is loaded into the active site of the enzyme, or the place that allows weak bonds to be formed between the two molecules. An enzyme-substrate complex is formed causing the substrate to react, and become the product of the intended reaction.

6.8 The bonds that form between the substrate and enzyme cause the conformational change, or shape change, in the enzyme. The resulting shape change is what applies pressure to the substrate, either forcing molecules together or tearing them apart. The specific bond in a substrate which can be broken by the enzyme is known as the scissile bond. In this way, enzymes act as catalysts to speed up chemical reactions by lowering the activation energy for the reaction to proceed. The lower activation energy means that the reaction can happen more quickly at physiological temperatures.

6.9 Many of the molecules in our bodies are substrate molecules, and there are a great range of enzymes which catalyse various reactions. Enzymes have a high degree of specificity: they will bind to one specific or class of molecules and usually catalyse only one type of reaction, commonly breaking the scissile bond in the natural substrate.

6.10 Inhibitors can be categorised into two types; as competitive inhibitors and non-competitive inhibitors, based on the place on the enzyme where the inhibitor binds. In competitive inhibition, binding of an inhibitor prevents the binding of the target molecule with the active site of the enzyme. In this inhibition type, the inhibitors that are bound to the active sites are similar to the shape of the substrate molecules (if not, the inhibitors cannot bind with the active site because the shape of the active site does not fit the shape of the substrate). Therefore, the enzyme active site cannot bind with both inhibitor and the substrate at the same time. This makes the inhibitor

compete with the substrate to bind to the active site, which gives the name competitive inhibition. As a very general principle, a reversible competitive inhibitor will need to 'outcompete' the natural substrate in order to prevent the natural substrate from being turned over i.e., the turnover number of an enzyme (kcat or catalytic rate constant) is the maximal number of molecules of substrate converted to product per active site per unit time of several different substrates to different products. This rate is proportional to the substrate concentration and is therefore designated first order.

6.11 In non-competitive inhibition, an inhibitor reduces the activity of an enzyme but does not bind to the active site of the enzyme. Instead, the inhibitor binds elsewhere on the enzyme and can bind even if the substrate is already bound to the active site of that enzyme. The non- competitor binds at what is called an 'allosteric' site. As the non-competitive inhibitor and natural substrate occupy different sites, there is no competition between the substrate and the inhibitor. Hence, this inhibition is known as non-competitive inhibition.

6.12 Serine proteases are a class of enzymes that cleave peptide bonds in proteins (hence the term 'protease'). Serine is an amino acid and, in serine proteases, it is the serine residue which plays an operative part in the enzyme's active site by serving as the nucleophilic amino acid. This means that the serine residue is an electron-rich species which has the ability to donate electron pairs and, in doing so, form bonds with electrophiles. Serine proteases are found ubiquitously in both eukaryotes (cells of animals including humans, plants and fungi) and prokaryotes (single-celled organisms that are the earliest and most primitive forms of life on earth, such as bacteria).

6.13 Factor Xa is a serine protease which cleaves prothrombin to generate thrombin and lies at the crossroads of the extrinsic and intrinsic coagulation pathway. Only a small amount of factor Xa is needed to generate many molecules of thrombin. Thrombin is also a serine protease and is itself involved in the clotting cascade. As referred to above, OPP-IV is a serine protease, as is trypsin,

6.14 Sequence homology is the biological homology between DNA, RNA, or protein sequences, defined in terms of shared ancestry in the evolutionary history of life. Homology among DNA, RNA, or proteins is typically inferred from their nucleotide or amino acid sequence similarity. Significant similarity is strong evidence that two sequences are related by evolutionary changes from a common ancestral sequence. Alignments of multiple sequences are used to indicate which regions of each sequence are homologous. The similarity in amino acid sequence of substrate structure would mean that the skilled person would be disposed to think that a compound which inhibits factor Xa might or would also inhibit another serine protease.

6.15 Enzyme inhibitors play a significant role in the drug discovery process and, as such, are common targets. Many disease states are explicable at the molecular level as caused by the dysfunction, overexpression, or hyperactivation of certain enzymes. This hyperactivation or overexpression of enzymes can be treated by using suitable enzyme inhibitors. Accordingly, drug discovery projects may be targeted towards identifying a suitable inhibitor of a particular enzyme. An example of an enzyme inhibitor that was in widespread use was captopril (sold under the brand name Capoten, among others), which is a highly specific, competitive inhibitor of angiotensin-1 converting enzyme (ACE inhibitor)....

[4] *Drug discovery process for enzyme inhibitors*

6.16 Enzymes and serine proteases at the Relevant Date were classes of drug discovery targets under active consideration.

6.17 Drugs that function as enzyme inhibitors constitute a number of orally bioavailable therapeutic agents that are in clinical use. Likewise, a large amount of drug discovery and development efforts are focussed on identifying and optimising drug candidates that act through inhibition of specific enzyme targets. The attractiveness of enzymes as targets for drug discovery stems from the high levels of disease association (target validation) and drugability (target tractability) that typically characterise this class of proteins.

6.18 Enzymes are essential, physiological catalysts involved in all processes of life, including metabolism, cellular signalling and motility, as well as cell growth and division. They are attractive drug targets because of the presence of defined substrate-binding pockets, which can be exploited as binding sites for pharmaceutical enzyme inhibitors. Understanding the reaction mechanisms of enzymes and the molecular mode of action of enzyme inhibitors is indispensable for the discovery and development of potent, efficacious and safe novel drugs.

6.19 The approach to the discovery and optimisation of inhibitors follows the traditional approach to drug discovery at this time-see 'General Points on the Drug Discovery Process' at paragraphs 6.28 to 6.38.

6.20 Potency is the desired activity of a compound in a compound screen. One way this can be expressed is as a Ki value, which is dissociation constant of an enzyme-inhibitor complex, which can be used to describe the binding affinity that a small molecule or macromolecule has for an enzyme. The lower the numeric Ki value is, the more potent (higher affinity) the compound has for the enzyme. At the Relevant Date, a drug discovery team undertaking searching for a potential drug (including a factor Xa inhibitor} would be looking for potency, as measured by Ki, in the low nanomolar or high picomolar-level range. Indeed, in every project that I have worked on including those pre-2001, the parameters for a drug which might be therapeutically useful were in the single-digit nanomolar range for the primary biological (enzyme) assay.

6.21 There were a number of reasons for setting this requirement. First, a higher potency drug can be given to patients in a lower dosage amount. This means that a smaller dose is given to the patient, so reducing the risk of undesired off-target pharmacology, leading to unwanted patient outcome. It will also reduce the Cost of Goods (CoG) to make the medication. Additionally, a higher potency can compensate for any other properties of the drug that may be sub-optimal, such as a comparatively low bioavailability but delivering the final drug requires a balance of properties (such as potency, oral bioavailability, solubility, etc). Having a compound as a drug candidate with a tow nanomolar K1 gives a better chance at delivering an effective medication, allowing, perhaps, a sub-optimal property in one or more of the other parameters being optimised, hence increasing the chances of delivering a new drug.

6.22 Second, if the target is an enzyme with a natural substrate and the medicinal chemist is seeking to develop a competitive inhibitor, the drug will in general have to displace the natural substrate at the active site of the enzyme. It is likely that the natural substrate has a high affinity for the enzyme, owing to the billions of years over which the two moieties have developed and been optimised together. At a general conceptual level, the potential drug will need to be as potent as the natural substrate to compete for the enzyme. The specifics of balancing these potencies would be a matter on which the skilled pharmacologist would take the lead.

6.23 Third, the primary biological assay in which the skilled medicinal chemist would be seeking low nanomolar potency differs from the in vivo setting in which the drug is intended to be used as a therapeutic. That primary biological assay does not recapitulate the physiological conditions the drug will encounter when in the body. For instance, when administered to humans, the drug will encounter plasma proteins in the blood. If, as is common, the compound exhibits some activity towards those plasma proteins, the free-drug concentration in the blood will be diminished. The Skilled Team would therefore typically perform a range of additional assays to further assess the compounds drug-like properties such as plasma protein binding. It is not uncommon to see a 10-fold shift to lower potency (lower affinity) in more disease- relevant assays as compared with primary biological assays.

6.24 Another key property is the selectivity of a drug. Selectivity can be thought of as: how many fold over the potency of the compound at another target (e.g., other serine protease) is the potency of the same compound at the desired target (e.g., factor Xa). For example, if the compound's potency at factor Xa is 1 nM (Ki) and 100 nM (Ki) at thrombin, it would be 100- fold selective over thrombin for factor Xa. It was common in 2001 to set a threshold for seeking 100-fold to 1000-fold selectivity in a potential drug for the target over other related enzymes. The exact figure is project specific.

6.25 In my experience of working on developing DPP-IV inhibitors, we worked on a 1000-fold selectivity over other structurally related serine proteases (e.g., DPP-8 and DPP-9).

6.26 In general terms, where the project is to develop an inhibitor against an enzyme which is structurally similar to other enzymes in the same class, the skilled medicinal chemist would have a concern that the inhibitor would display activity against other such enzymes. In the case of factor Xa, serine proteases are a family of related proteins with similarities in their active sites. If a drug was suitably potent against factor Xa, the skilled medicinal chemist would have an expectation that binding to other (off-target serine) proteases would likely result. This binding to other serine proteases would likely be something the project would want to avoid with active compounds. Selectivity is a very important property, much like potency, and selectivity assessment would be part of the initial screening of compounds.

6.27 Other drug-like properties: In order for the molecule to move through the testing paradigm and be confirmed as the drug candidate, the compounds must be tested in other assays to ensure that the compounds have the necessary biological, pharmacological and physiochemical properties. Thus, the compounds would pass through physiochemical determination of properties such as lipophilicity (how water loving/hating is the compound), its solubility, metabolic stability, ability to cross membranes, any activity at cytochrome P450s, for example. The compound may then be tested to assess its pharmacokinetic properties in rodents and also to determine an effect on clotting.

[5] *General points on the drug discovery process*

6.28 Drug discovery is an expensive and time-consuming undertaking. It typically occurs as a staged process in which the Skilled Team is initially looking for compounds that act as a starting point (having some degree of activity against the target) through to optimising and refining the chemical structure of a compound, which may become a clinical candidate.

6.29 The process is generally iterative. The medicinal chemist will synthesise a series of compounds and, with the skilled pharmacologist, examine and

analyse their characteristics, including potency and selectivity. More promising drugs advance from initial in vitro assays to testing in animal models and eventually humans.

6.30 Making modifications to the chemical structure can cause significant and unpredictable changes to the properties of the compound. Even apparently small chemical changes can have material effects. By way of example:

6.30.1 The so-called Magic Methyl Effect: "a rare but welcome phenomenon" where installation of a methyl group on a molecule leads to an increase in potency, arising, in part, from a drastic change in conformation, hence, binding affinity. Examples include methylation of a hydroxyl group in morphine to produce codeine, or removal of a methyl group (N-Me) in morphine to give normorphine. Similarly, adding a methyl group to 'Benadryl' ta give Toladryl' provided a compound with a 3.7-fold increase in activity and a 2.5-fold decrease in anticholine activity.

[Image Not Included in Judgment Text]

6.30.2 Addition of a fluorine group can have a major effect on potency and many other properties. For example, the compound on the right (R is benzyl) was used to explore interactions in the active site of the serine protease, thrombin. The 4-fluorobenzyl analogue exhibited 5-fold better inhibition (K 57 nM) compared to the benzyl derivative (K1 270 nM).

[Image Not Included in Judgment Text]

6.30.3 Enantiomers are a pair of molecules that exist in two forms that are mirror images of one another but cannot be superimposed one upon the other. Enantiomers are in every other respect chemically identical. A eutomer is the chiral enantiomer having the desired pharmacological activity, e.g., as an active ingredient in a drug. The distomer on the other hand, is the enantiomer of the eutomer which may have undesired bioactivity or may be bio-inert. It is often the case that only a single one of the enantiomers contains all of the wanted bioactivity, whereas the distomer is often less active, has no desired activity or may even be toxic.

6.31 As a result, the skilled medicinal chemist would always need to test a new compound's potency and selectivity when they have made changes to the chemical structure. Small, single, changes in structure can have a large effect on potency and/or selectivity; for examples, see above, such as the 'magic methyl' effect. It is therefore necessary to test for both throughout the project.

6.32 The initiation of a drug discovery project frequently starts with biologists assessing targets that may have relevance to a specific disease and whether the development of assays to assess chemical compounds' activity against this relevant target would be feasible. Clinicians (medical doctors) would be involved early on assessing what requirements a drug would need to have to meet patients' needs and to become successful, producing a Target Product Profile ('TPP'). Often a health economic assessment is applied early on to help assess the suitability of any disease approach to be economically successful in the marketplace and this is important to help discriminate between multiple new target initiatives in a pharmaceutical company's portfolio.

6.33 I have been involved in all of the above phases of drug discovery, in leading projects (e.g., OPP-IV enzyme inhibitors). The description that I provide is based on my experience of developing small molecule enzyme inhibitors and that the same principles apply between different enzyme targets. I have been

involved as a project member from the Hit to Lead, candidate nomination to the clinical phases.

6.34 Biological Assays:

6.34.1 The biologist would decide on a panel of relevant biological assays, to determine if candidate compounds have the necessary properties to be potentially useful and taken forward in development. They would, for example, develop the primary biological assay (at that time often an isolated biochemical assay where success against the disease was considered to be driven, in large part, by activity against the biochemical target). With relevance to the present patent, this would be factor Xa. A pharmacologist would be involved at an early stage to assess the suitability of the target selected and to assist with development of disease relevant animal models to test compounds against and so help assure the success of the project.

6.34.2 There are a number of different ways the project could be furthered, depending on the project, and these would stem from the available start points (in combination or alone, depending on what is possible) to provide chemical start points for initiation of 'wet chemistry' efforts in the laboratory. Thrs, in turn, would depend on the state of the field ln the relevant area. Are there lots of published compounds or do we have to start with a Hight Throughput Screen ('HTS') and see what actives are identified? Below I discuss compounds arising as active against a biological target from a HTS and that these would be valuable starting points for the skilled medicinal chemist to consider. The ideal with running a HTS is · that large numbers of compounds are screened (ca. 106) and so there should be a good chance of finding hit compounds. Given that drug-like space may contain orders of magnitude more theoretically possible compounds (up to ca. 1060), this isn't always the case.

6.35 Library Screening:

6.35.1 The biologist would, with the help of the screening group, screen the pharmaceutical company's deck of screening compounds (sometime called a screening file) in a HTS, which would be around a million compounds. A HTS is run where the biological assay developed initially is worked up into a format (96-well plate used) to parallelise screening and allow testing of potentially millions of compounds over a relatively short time scale. This requires specialists to utilise automation to facilitate this process. The level of stewardship of this file in terms of, for example, assessment of compounds drug-like properties, ensuring they are pure, removal of frequent hitters (compounds arising as active in many screens that containing undesirable chemical groups that prove unoptimisable in drug discovery), etc, varies from company to company. Generally, if assay and resources permit, the whole file would be screened. Sometimes the screening can be 'front loaded' with a cherry-picked set of compounds contained within the file, or bought and added to it, if there were reasons to suppose these compounds would be more likely to deliver hits from the screening effort. The biologist would interpret the assay results to ensure that the data generated supports real, bona fide hits being identified from the assay. The biologist would be generally trying to identify compounds with a potency of less than 10 micromolar in the assay. Other factors and assays would be utilised, for example, to remove compounds that may be toxic to cells, and to remove compounds with less than a certain window of selectivity against other (serine protease) targets, for instance. Thus, a list of active compounds

would be provided by the biologist to the Skilled Team and, in particular, to the medicinal chemist, for taking further.

6.36 Structure Based Drug Design:

6.36.1 A further start point is to use computational approaches to source literature published x-ray structures, ideally with the protein and potential inhibitor compounds bound, to use in protein docking studies with a computerised list of compounds (commercial, in house) to see if any in silica predicted hits arise. This approach arises if, as likely, there are x-ray structures available of the enzyme to assist with structural based drug design efforts. If commercial, these compounds can be bought in and tested in the biological assays. If no published x-ray is available, the project may attempt to develop this in house, or use other techniques to determine potential binding events of compounds against the target. This could include developing a homology model (noting features of related proteins against factor Xa in this instance and designing an approximation for factor Xa), which is used to dock compounds from the collection into and discover potential active compounds.

6.36.2 Further, literature start points (from a search of the literature) could be used as start points for drug discovery; to understand these compounds and to take them forward. This phase is led typically by the medicinal chemist.

6.37 Structure Activity Relationships:

6.37.1 SAR can be used as the basis for the next round of medicinal chemistry design. This powerful technology is used in drug discovery to guide the acquisition or synthesis of desirable new compounds, as well as to further characterise existing molecules. This is because similar compounds may have similar physical and biological properties. SAR depends on the recognition of which structural characteristics correlate with chemical and biological reactivity. Thus, the ability to draw conclusions about an unknown compound depends upon both the structural features that can be characterised, as well as the database of molecules against which they are compared. Typically, one might start by seeking to understand the effects of a single point change, e.g., sequentially extending an alkyl chain, add in a methyl group, etc. In terms of compound numbers required to undertake an SAR analysis, you might start with, say, 6 compounds in a series and build out SAR from these compounds. You may have a situation with 50-100 compounds (and their respective data) generated, with changes across several areas of the molecule, to cover an appreciable amount of the compounds chemical space, which can be utilised further in developing the SAR. These compounds are assessed by the medicinal chemist so as to ascertain patterns of SAR in the data. This will include inspecting the chemical structure and looking for patterns in the data generated, for instance does potency correlate with the compounds lipophilicity, which would generally be considered a bad thing. Confidence in the choice of newly designed compound for synthesis in the next round would be higher if a 'within series' change is contemplated, i.e., if you have data for the methyl, ethyl, butyl analogues and want to make the propyl analogue, this interpolation of results would lead to a higher likelihood in obtaining an expected result than if, for example, you make a more drastic (template) change.

6.38 Medicinal Chemistry:

6.38.1 The medicinal chemist would assess whether the compound is considered a 'singleton', with no related structures. In this case, it is necessary to assess whether this is a 'real' hit in the assay. Typically the medicinal chemist would design and synthesis a number of close analogues, making one change at a time (addition of a methyl group, removal of the same, add/change a heteroatom, etc). Each compound(s) would be assessed for its level of biological activity in relevant biological assays, to determine the effect of the structural change on the activity of the compound. If activity is maintained, this original compound(s) may remain interesting to the medicinal chemist. If not, the compound is likely discarded. A number of compounds would be re-synthesised (particularly if arising from a HTS or commercially}, to ensure the test article is pure and biological activity is not derived from an impurity. Computation approaches are also used to compare compound properties and use received opinion (such as Lipinski's 'Rule-of-5') to help determine which compounds to make.

6.38.2 Further compounds would be designed and synthesised (in the design, synthesise, screen, interpret results - leading to the next round of design in the iterative closed loop) to determine which compounds or series of related compounds are the most suitable to progress in drug discovery. Data would be gathered on the compounds to assess their on-target (factor Xa here) activity, any off target activity not wanted (e.g., lack of selectivity over other related enzymes, or cellular toxicity), physiochemical properties (solubility, lipophilicity) and the compounds Absorption, Distribution, Metabolism and Excretion (ADME) properties, such as Phase I and Phase II metabolic stability. As a general rule, the further along the drug discovery process the compound/series is, the more data is gathered on a compound. There may be some initial pharmacokinetic analysis in rodents performed .on compounds at late Hit-to-Lead stage, in order to confirm some sufficient properties on the compound in an animal, such as initial bioavailabilty testing.

6.38.3 Once the (multiple) series of compounds are assessed, one or two {depending on what remains and project resourcing available) will be chosen based on having the best overall properties in all the biological and physicochemical assays carried out. This series will be taken into LO. A prudent research team may decide on a Lead series and back-up series, typically structurally distinct from the lead series to ameliorate project risks derived from structure. Essentially, the team would not want to put all their eggs in one basket. while also not being able to take forward every potentially interesting compound/series.

6.38.4 The project with its "design, synthesise, screen, design" iterative loop obtains data on compounds designed and synthesised. Skilled Biologists/Pharmacologists are in charge of screening and interpreting biological data and the skilled medicinal chemist is charged with compound design and synthesis and interpretation of results. Compounds are tested in multiple assays and the data interpreted, leading to new compounds designed. This cycle repeats over, typically, 18 months to around three years until it delivers a clinical candidate. This candidate molecule has the properties (in vitro and in vivo) believed to be capable of providing a successfully marketed drug.

6.38.5 There are different ways in which an inhibitor and an enzyme can interact which are described in more detail below:

(a) *The ways in which an inhibitor and an enzyme interact are manifold. Strong interactions result from formation of a covalent bond between the enzyme and the inhibitor. Depending on the type of covalent interaction the binding can range from readily reversible to effectively irreversible. An array of weak interactions also allow and facilitate inhibitor binding to enzymes.*

(b) *One such interaction are van der Waals forces, which are a distance- dependent interaction between atoms or molecules. Unlike ionic or covalent bonds, these attractions do not result from a chemical electronic bond. They are comparatively weak and therefore more susceptible to disturbance. The van der Waals force quickly vanishes at longer distances between interacting molecules. Van der Waals forces are weak electrostatic forces that attract neutral molecules to one another. It provides for an attractive interaction between atoms, which results from the induced dipoles, and a repulsive interaction, which results from overlap of the electron clouds of the two atoms, when they get too close to each other. This attraction, with suitably substituted compounds; allows an inhibitor to bind to an enzyme. Other forces are at work in binding.*

(c) *lntramolecular Hydrogen bonding play a crucial role in determining the specificity of ligand binding. A hydrogen bond (or H-bond) is a primarily electrostatic force of attraction between a hydrogen (H) atom, which is covalently bound to a more electronegative atom or group (such as oxygen or nitrogen) and another electronegative atom bearing a lone pair of electrons - the hydrogen bond acceptor (Ac). Hydrogen bonds can be intermolecular (occurring between separate molecules) or intramolecular (occurring among parts of the same molecule). Inhibitors will often contain the correct atoms to undergo hydrogen binding with the residues lining the binding pocket and so stronger binding ensues.*

(d) *A salt bridge is another type of interaction seen upon inhibitor binding. A salt bridge can be defined as an interaction between two groups of opposite charge in which at least one pair of heavy atoms is within hydrogen bonding distance {for example, arising from NH3+-CO2- interaction of amino acids). Salt bridges can contribute to protein stability and to conformational specificity, as well as in positioning critical functional groups.*

(e) *The inhibitor will exist in a 'biologically active' conformation (3D-shape) that has a complementary geometry to the features of the enzyme's binding pocket, namely the Lock and Key Hypothesis. In 1894, German chemist Emil Fischer proposed this lock and key theory, which states that enzymes have a specific*

shape that directly correlates to the shape of the substrate. Basically, substrates fit into an enzyme the way a key fits into a lock. Thus medicinal chemists will often try to rigidify the molecule, for example through incorporation of a template core within the compound, which puts the groups that interact with the enzyme into a favourable conformation for binding....

[6] *Factor Xa inhibitors*

6.39 In order to place myself in the position of the skilled medicinal chemist in 2001 joining a factor Xa drug development team in 2001 I carried out a literature search. The skilled medicinal chemist would join a new project team without necessarily specific knowledge of the therapeutic area or target. As a result of this, they would discuss these with other members of the project team, or the Skilled Team as defined above, as well as carry out literature searches to identify publications which may assist with developing this relevant knowledge and understanding.

6.40 Accordingly, l used PubMed as a search tool for my literature searches. PubMed was widely available in 2001 and the skilled medicinal chemist and Skilled Team would have regularly used this database to locate relevant scientific papers. As the skilled medicinal chemist would have been interested in obtaining papers more broadly about factor Xa, whilst still focussing on the aim of developing a small molecule inhibitor, I therefore ran a literature search which initially returned 2,196 results. I ran a further search to narrow down the number of results. With both searches, the date range used was 01/01/1970 to 31/12/2001, in order to capture as many relevant references as possible prior to the end of 2001 date. This second search returned 18 results. From this list, I reviewed each title and identified papers of interest to the skilled medicinal chemist based on the relevance of the title to the development of factor Xa inhibitors.

6.41 I provided the list of results to Pinsent Masons {Ireland) along with a list of the 11 papers I identified as being of particular interest to the skilled medicinal chemist. The list of the 11 papers are set out [in Dr Edwards' unabridged witness statement]....

6.42 From my review of the 11 papers, I identified certain recurring themes or topics which would have been considered the CGK. I have explained these below and discussed the key takeaway points for the skilled medicinal chemist.

6.43 General summary of the state of the field:

6.43.1 From the papers, it appears that, prior to 2001, there were a number of companies involved in factor Xa research, including Daiichi Sankyo Inc (formerly Daiichi) with DX9065a (Ki 40 nM)1, Pfizer, Rhone Poulenc Roher (RPR) and Aventis, with FXV672; Ki 0.5 nM for factor Xa and more than 1,000-fold selectivity over thrombin, activated protein C, plasmin and tissue-plasminogen activator. The literature at that time described factor Xa inhibitor compounds with potencies (as measured by Ki) in the low namomolar to picomolar range. The skilled medicinal chemist would take from this that high potency compounds and series of compounds had, by 2001, been achieved. Additionally, some of the papers discuss certain compounds having high selectivity (>1,000-fold) over related serine

proteases, e.g., thrombin, also suggesting that factor Xa selectivity has been achieved by 2001.

6.44 Structure of factor Xa:

6.44.1 The enzyme active site has various pockets and two of relevance are the 'S1' and 'S4' pockets.

6.44.2 The active site of factor Xa comprises three main areas used in substrate recognition and several side pockets. Most of the active site lies on the surface of the protein with the exception of the so called 'S1' pocket, which extends deeply into the core of the protein. The S1 pocket is the main anchoring point and can accommodate a positively charged lysine or arginine side chain from the substrate ('P1') residue. It is a narrow cleft with planar hydrophobic walls (hence hydrophobic substituents such as aromatic rings are tolerated) and a negatively charged amino acid that engages in a salt bridge with substrates, which lies at the bottom of the pocket. The pocket is somewhat larger than the lysine or arginine side chain and can accept bulkier groups, such as aromatic rings. The main difference between the S1 pocket of factor Xa and thrombin is residue 190, which is alanine in factor Xa and thrombin, but a serine in trypsin. This change modulates volume and electrostatic properties of the pocket. Another important feature of the S1 pocket is the presence of a buried water molecule located above a particular amino acid residue.

6.44.3 The 'S4' pocket consists of a surface cleft with hydrophobic residues as the floor and walls. It usually accommodates a hydrophobic residue but it has been recognised that the aromatic side chains of several amino acid residues can participate in favourable interactions with a positive charge. Additionally, the carbonyl oxygen atoms of several amino acids, and the side chain of a further amino acid at the periphery of the S4 site, further stabilise a positive charge in this region. This 'cation hole' has been invoked to explain the potency of inhibitors with positively charged/or basic groups at the 'P4' position.

6.44.4 Selectivity is often achieved by interaction with the S4 pocket, since it differs significantly from most trypsin-like serine proteases, although the tissue type plasminogen activator (tPa) S4 pocket differs from factor Xa by only one residue, making the achievement of selectivity over all members of the serine protease family a challenge.

6.45 Structure of factor Xa compared with other serine proteases:

6.45.1 From the papers, it is clear that there is a significant degree of homology between factor Xa and other members of the serine protease family of relevance. This means, if the sequence of amino acids lining similar binding regions of several serine proteases are the same, such as the binding pockets (i.e., S1/S4), designing compounds which differentiate between serine proteases is challenging. Thus, selectivity can be difficult to achieve. In some cases, some residues do differ, so forming the basis for selectivity between different serine proteases.

6.46 Compounds of interest

6.46.1 Based on the papers, DX-9065a is an early example of a potent factor Xa inhibitor, displaying a Ki of 40 nM for factor Xa, with good to excellent selectivity versus thrombin, trypsin and other serine proteases of interest. This compound is highly basic as it contains amidine groups, which drives

potency against factor Xa to an extent, but also imparts poor drug-like (e.g., oral bioavailability) properties. Thus, even with a good Ki value, this compound did not display good pharmacokinetics. Attempts to overcome these problems with bioavailability have run along lines of removing or reducing the basicity of groups, removing the peptidic nature of early inhibitors in subsequent synthesised compounds. Knowledge of structural data has been instrumental in assisting with designing potent and selective compounds, but this does not provide any certainty that a compound will actually be potent and selective and it also does not provide certainty on how to improve pharmacokinetic parameters. For the skilled medicinal chemist to be sure that a compound is potent, selective and has good pharmacokinetic properties, the compound would need to be made and tested.

6.46.2 Other compounds which would be of particular interest from the papers include those from Rhône Poulenc Roher (RPR; RPR208566; Ki 1.3 nM, selectivity fll >4,000-fold and selectivity over thrombin 185-fold. Also RPR-120844 Ki 7 nM, with fXa selectivity over thrombin at 140-fold, over trypsin (76-fold), overt-PA {>1,000- fold) and over aPC {340-fold)) and Bristol-Myers Squibb (DPC-423; Ki 0.1SnM. Kl [nM] for the following: trypsin, 60; thrombin, 6000; plasma kallikrein, 61; activated protein C, 1800; factor IXa, 2200; factor VIia, >15,000: chymotrypsin, >17,000; urokinase, >19,000; plasmin, >35,000; tissue plasminogen activator, >45,000).

6.47 General structures of compounds in the field:

6.47.1 The most common P1 group is the benzamine, which is highly basic. The group incorporates necessary features to form strong interactions in the S1 pocket, useful to factor Xa design.

6.47.2 From a medicinal chemistry design perspective, the phenyl ring provides the right size to place the amidine deep inside the pocket and still presents potential sites for derivatisation, which can extend design to other regions of the active site. The aromaticity and planarity of the phenyl ring matches nearly exactly the shape and hydrophobic characteristics of the pocket. Benzamide containing inhibitors are modelled into the S1 pocket.

6.47.3 Nevertheless, in some cases this assumption is wrong (the compounds display a 'reverse binding') and only an experimental structure determination provides an unequivocal answer.

6.47.4 A great diversity in reported factor Xa inhibitors is seen in the P4 group. In most cases, the P4 group displays hydrophobic and aromatic character. Sometimes a polar group is added, for example to enhance the physiochemical properties of the molecule. The benzamide group is a P4 group. There is an example of a o.- ketoamide series of compounds (Du Pont utilising a nitrile group as a P4 group, which reverses selectivity from thrombin-selective to factor Xa selective. There is no obvious explanation for this. Motjelling suggests that bulkier groups and more polar groups could make improved interactions in this pocket, but SAR proved otherwise, suggesting that the models do not have a predictive power in this case).

6.47.5 Selecting the central linker or scaffold connecting P1 and P4 has significant implications dictating the synthetic pathway and medicinal design of compounds. Unlike P1 and P4 substituents, whose characteristics ought to compliment those of the pocket, the main role of the scaffold is spatial and conformational; providing a template to project P1 and P4 groups into their respective pockets at an optimal distance and orientation. This has led to great structural diversity both in terms of chemistry and physiochemical properties. This can mean that the scaffold/linker may be flexible (to allow

groups to 'seek' their optimal binding) or a rigidified scaffold (where groups are 'told' where to sit, which allows binding to the pocket). Variable potency and selectivity would arise from the differing linkers/scaffolds used.

6.47.6 From the published models and structures of factor Xa inhibitors, it is possible to draw the following conclusions: that factor Xa inhibitor models are usually (though not always) in good agreement with experimentally-determined structures as regards the likely binding mode of the inhibitor in factor Xa. ln some cases, however, unexpected binding modes are seen and 'reverse binding' can be seen also.

[6] *...Analysis of PCT/US99/30316 (WO00/39131A1) and WO03/026652A1....*

[i] WO652

7.1 *I was first provided with and asked to consider WO131, followed by WO652, and to describe what each document discloses to the skilled medicinal chemist reading these in 2001 in light of the CGK set out above. There are overlaps in my comments in relation to WO131 and WO652 and so for the purposes of this report, I set out my views on WO652 first and where relevant, I cross refer to this WO652 section in my analysis of WO131 at paragraphs 7.28-7.38 below.*

Title, Abstract, Field of the Invention and Summary of the Invention

7.2 The skilled medicinal chemist would understand that WO652 relates to lactam containing compounds and derivatives as inhibitors of trypsin-like serine protease, in particular against factor Xa, to be used in the treatment of thromboembolic disorders. This is set out in the Title, Abstract, Field of the Invention and Summary of the Invention at page 7, lines 2-5, 11-16 and lines 30-32 to page 8, line 5.

7.3 The skilled medicinal chemist would be aware of lactams since they are commonly used in chemistry and drug design. A lactam is a chemical ring system. lt is a cyclic amide where the amide has one or more carbon chains connecting the carbonyl carbon to the nitrogen atom, see picture. There are examples of drugs on the market which include a lactam group, including the class of antibiotic penicillin derivatives (penicillin, ampicillin; beta-lactam ring). Cephalosporins- derived antibiotics also contain a lactam ring. The skilled medicinal chemist would therefore not be surprised that a lactam is included in a potential factor Xa inhibitor.

[Image Not in Judgment Text]

7.4 A lactam ring, when compared to the open-chain analogue has less degrees of (bond) rotational freedom and this more constrained conformation could lead to an increase in potency for analogues containing the lactam ring. The conformational fix may increase desired potency and affect selectivity.

7.5 I note that the skilled medicinal chemist is not told in these early sections where the lactam should be located, and in particular, where it should be located for a compound to have activity against factor Xa. Later in the document, there are a number of complex Markush formulae which cover a large number of potential compounds. These make it very difficult for the skilled medicinal chemist to work out where the lactam or its derivative should be positioned. The skilled medicinal chemist could make the assumption that the lactam could be (substituted or unsubstituted) the B ring in a 1,4-substituted relationship in A-8 in WO652, as can be seen on page 117, line 5 of this patent, which provides for preferred embodiments with this 1,4 relationship.

7.6 Although the specified lactam-containing compounds are of the Formula I, which is P4-P-M- M4, present as a pharmaceutically acceptable salt or prodrug and said to be effective factor Xa inhibitors, as I discuss further below, from the disclosure in WO652, I do not think that the skilled medicinal chemist would be able to come to the conclusion that the compounds of WO652 are actually effective factor Xa inhibitors.

7.7 Background of the invention (pages 1-6)

7.8 The Background of the Invention section starts off with a list of patents and patent applications. This list is split between those patent and patent applications which are said to not relate to factor Xa (from page 1, line 15 to page 2, line 17) and those which do relate to factor Xa (from page 2, line 18 to page 5, line 20). It is explained that the compounds covered by the patents or patent applications in this latter list are not considered part of this invention. As the patents and patent applications listed are not considered relevant to the invention, I do not think the skilled medicinal chemist would have reviewed these documents.

7.8.1 From page 5, line 21, WO652 discusses the role of factor Xa in the coagulation cascade and explains that activated factor Xa's major practical role is the generation of thrombin by limited proteolysis of prothrombin". It goes on to explain that the inhibition of factor Xa may be more efficient than thrombin in interrupting the blood coagulation system. This is the rationale provided for targeting factor Xa over thrombin.

7.8.2 It then goes on to state, on page 6, lines 6-8, that "efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders." The skilled medicinal chemist would understand "efficacious" to be partly defined by the potency, but also the physical chemistry and pharmaceutical properties, i.e., they would be looking for the drug to have the desired therapeutic effect in an animal model and in humans at the appropriate dose. The skilled medicinal chemist would understand "specific" to mean that the compound only inhibits factor Xa with a specified higher potency than other enzymes. Despite stating here that specific factor Xa inhibitors could be valuable therapeutic agents for thromboembolic disorders, I do note that later in the document, there is also, confusingly, discussion of thrombin inhibition.

7.8.3 W0652 goes on to state, on page 6, lines 9-12, that "{i]n addition, it is also desirable to find new compounds with improved pharmacological characteristics compared with known factor Xa inhibitors", and then lists a number of categories and associated factors relating to these pharmacological characteristics.

7.9 These relate mainly to Drug Metabolism Pharmacokinetic (DMPK) properties, which are outside my area of expertise. This is a standard write-up of the principles required for an efficacious agent and there is no data in the patent to substantiate these wants. The skilled medicinal chemist in 2001 could not predict if any compounds of the invention meet these properties from their names/structures alone and so there would be a need to test the compounds to determine this.

Detailed Description of Preferred Embodiments (page 8-134)

7.10 The Detailed Description of Preferred Embodiments section describes the compounds and the use of these compounds which the skilled medicinal chemist would understand to represent the present invention.

7.11 There are over 100 pages of Markush formulae and 20 pages of lists of compounds. The Markush formulae are complex and cover millions upon millions of possible compounds.

7.12 The invention is expressed in general terms as an array of compounds of the general Formula I. The G group is then further defined as two combinations (Formula Ila and Formula lib) of rings D and E. The decorating groups provide for a broad scope of chemical space claimed. The patent application claims a wide array of cores, for example with ring 'M' starting on page 30.

7.13 For all of the embodiments set out in WO652, none of them provide any explanation or rationale for the selection of any of the groups. It also does not place any emphasis on whether particular parts of the molecule are especially important for binding to factor Xa. WO 652 does not provide any explanation of how the compounds encompassed within the embodiments might bind to factor Xa in order to justify that they could be factor Xa inhibitors. Instead, it is just a list of broad and complex Markush formulae. There is also no explanation of why each of the later embodiments are "preferred", nor is any rationale given for why the selections have been made. The skilled medicinal chemist would find it impossible to accurately define the scope of the compounds given the huge number and complexity of the Markush formulae described in the embodiments, and is not taught anything, explicitly or implicitly, about which compounds may be preferred from within the vast array disclosed.

Synthesis (pages 143-168)

7.14 The Synthesis section sets out the routes for the preparation of some of the groups of molecules that fall within the Markush formulae described above. The skilled medicinal chemist would recognise that the experimental write-up is standard. All reactions were known in the literature at that time and would have been known to the skilled medicinal chemist in 2001.

Utility (pages 168-188)

7.15 The skilled medicinal chemist would expect the Utility section to set out the biological activity and utility of the compounds covered by WO652. Useful biological activity data wou[d include the compounds' in vitro potency and selectivity, DMPK data and in vivo data, such as bioavailability and efficacy in an appropriate animal model.

Potency

7.16 From page 169, line 22, the utility section describes an in vitro chromogenic assay that may be used to test for inhibition of purified factor Xa. The skilled medicinal chemist would be familiar with the use of chromogenic assays to measure the activity of enzyme inhibitors more generally. Such assays are commonly used in drug discovery to generate K1 values in the initial stage of a screening cascade. Conducting an in vitro assay against the target enzyme would be a standard step when investigating potential inhibitors.

7.17 On page 170, lines 21-32, WO652 goes on to state:

'Compounds tested in the above assay are considered to be active if they exhibit a K, of$ 10 µM. Preferred compounds of the present invention have Ki's of 75. 1 µM. More preferred compounds of the present invention have K's of s; 0.1 µM. Even more preferred compounds of the present invention have K;'s of::.

0.01 µM. Still more preferred compounds of the present invention have K;'s of s 0.001 µM. Using the methodology described above, a number of compounds of the present invention were found to exhibit a K; of$ 10 µM, thereby confirming the utility of the compounds of the present invention as effective factor Xa inhibitors.'·

7.18 This is the only information within the whole of WO652 provided on the results from this in vitro chromogenic assay. WO652 does not state which of the compounds covered by WO652 have been tested in this assay and found to have a Ki s 10 µM. From this data alone, it would be impossible for the skilled medicinal chemist to know which compounds had been tested as inhibitors of factor Xa and what activity they had.

7.19 The section also states that compounds 'are considered to be active if they exhibit a Ki of s10 µM' and that 'a K1of-5. 10 µM [confirms] the utility of the compounds of the present invention as effective factor Xa inhibitors.' As discussed in the CGK section above, drug development teams were looking for compounds with a K1 in the low nanomolar or even picomolar ranges. The skilled medicinal chemist would therefore be surprised by the assertion that a compound with a K1 of 1O µM is an 'effective factor Xa inhibitor'.

Selectivity

7.20 There is no data in W0652 as to the selectivity of the compounds disclosed. As discussed above, W0652 states that "specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders." On page 171, at lines 18- 21, it describes how "compounds of the present invention may a/so be useful as inhibitors of serine proteases, notably human thrombin, Factor VIia, Factor /Xa, Factor Xia, urokinase, plasma kaflikrein, and plasmin." The skilled medicinal chemist is not told, and cannot work out from the disclosure in the document, to which, if any, of the compounds disclosed in WO 652 this statement applies. Additionally, it says the compounds "may also be useful" suggesting that potency against these compounds has not been ascertained. Potency against these enzymes would be of interest to the skilled medicinal chemist since it would tell the skilled medicinal chemist which compounds might or might not be selective for factor Xa, which, as explained above, is highly desirable.

7.21 On page 171, from line 31, it describes how '[s]ome compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin' and describes the in v;tro chromogenic assay used to demonstrate this. The paragraph concludes that '[u]sing the methodology described above, some compounds of this invention were evaluated and found to exhibit a Ki of Jess than 10 µM, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors'. As described above in relation to factor Xa, the skilled medicinal chemist does not know which compounds have been tested. However, this statement suggests that some compounds are not specific for factor Xa and also inhibit thrombin. This would be an area of concern for the skilled medicinal chemist for the reasons set out above regarding the need for selectivity.

7.22 Overall, there is no data for any of the compounds to inform the skilled medicinal chemist whether any of the compounds disclosed are selective for factor Xa or that the selectivity of the compounds has even been considered.

In vivo data and DMPK properties

7.23 The skilled medicinal chemist would be interested in data describing in vivo activity as in vitro activity does not always equate to in vivo efficacy. The skilled medicinal chemist would also be interested in the DMPK properties of the compounds, which would assist in determining which of the compounds were suitable for further testing.

7.24 There is no information about the DMPK properties of the compounds disclosed.

7.25 On page 170, line 33, it describes a rabbit arterio-venous shunt thrombosis model and it states that this model can demonstrate the antithrombotic effects of the compounds. I am not familiar with this particular model and would consider this with a pharmacologist. No results are given for this animal model and that there is no suggestion that any of the compounds disclosed in W0652 were actually tested in this model. For cost and ethical reasons, animal experiments are normally only performed on compounds that have demonstrated good potency and selectivity in vitro, as well as other DMPK properties. As explained above, it is not clear that any of the compounds in W0652 demonstrate this. The skilled medicinal chemist may therefore assume that the compounds in W0652 have not been tested in this animal model.

Examples (pages 188-315)

7.36 The Examples section sets out 140 examples. The skilled medicinal chemist would note that no structures are provided and that there is no data describing activity against factor Xa or any other serine proteases. The syntheses of these compounds are described in variable detail and some characterisation data is provided in the form of reported peaks from nuclear magnetic resonance ('NMR') spectroscopy, and/or low or high resolution mass spectrometry ('LRMS' and 'HRMS', respectively), following purification by high performance liquid chromatography ('HPLC') (together 'LC/MS'). Based on this data, the skilled medicinal chemist would understand that these compounds have been made and purified.

7.27 Following those 140 examples,· there are a series of tables containing 'representative examples'. No syntheses information and no characterisation data are provided....

[ii] *W0131*

7.28 As mentioned above, I was asked to consider what WO131 teaches the skilled medicinal chemist in light of their common general knowledge. I understand that, when considering WO131, the skilled medicinal chemist will not have in mind the contents of WO652. Indeed when I first reviewed WO131, I had not looked at WO652. However, it is apparent to the skilled medicinal chemist that there is a very high degree of similarity between the two documents. I have therefore been told that I can focus my report on sections of WO131 that differ from those of WO652.

Overview

7.29 The skilled medicinal chemist would understand that WO131 is directed to various compounds that are based on nitrogen-containing heterobicycles, which are said to be factor Xa inhibitors to be used in the treatment and prevention of thromboembolic disorders. This is set out in the Title, Abstract, Field of the Invention and Summary of the Invention sections.

7.30 The skilled medicinal chemist would be aware of nitrogen-containing heterobicycles. They are commonly used within medicinal chemistry. A heterobicycle is made from two fused carbon rings and contains at least one heteroatom in at least one of those rings, in this case, with nitrogen-containing heterobicycles, at least one of which would be nitrogen.

Background of the invention (pages 1-2)

7.31 This section lists patents and patent applications that are said to disclose nitrogen-containing heterobicycles, but which are said not to be relevant to the present invention. As such, the skilled medicinal chemist would not be interested in reviewing these documents.

7.32 From page 2, line 11, it describes the role of factor Xa in the coagulation cascade and the reason for targeting factor Xa instead of thrombin to prevent blood coagulation. It concludes with the same statement as WO652: 'efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors'. My views on this are set out in relation to WO652 at paragraphs 7.8.1 - 7.8.3.

Detailed description of preferred embodiments (pages 3-57)

7.33 This section describes the compounds that are embodiments of the present invention and the use of these compounds.

7.34 As with WO652, the description of these compounds is by Markush formulae, and a list of compounds spanning 53 pages without any explanation for why these specific compounds have been described. As with WO652, the Markush formulae are very broad and complex and the number of compounds is so vast that it is impossible to assess accurately. Also, as with WO652, no justification is given. for selecting the compounds that fall within these Markush formulae. There is no explanation of which parts of the compounds are important for binding to, and thus inhibiting, factor Xa nor any accompanying description to explain why any particular parts of the vast and extremely broad Markush formulae are important for, for example, potency and selectivity.

Synthesis (pages 63-96)

7.35 As with W0652, the chemistry described in WO131 would have been well known to the skilled medicinal chemist in 2001.

Examples (96-262)

7.36 This section contains 109 named examples with structures. No biological data is provided for any compound.

Utility (pages 263-272)

7.37 The Utility section of WO131 is very similar to that of WO652. As I have explained above, the skilled medicinal chemist would be interested in data on potency, selectivity, in vivo efficacy and bioavailability in relation to the compounds disclosed.

7.38 For the most part, the utility section dealing with potency and selectivity and in vivo assays are identical to those in WO652. The skilled medicinal chemist would note that there are some immaterial differences relating to the

chromogenic substrate used in the factor Xa assay, the order of some of the text describing the factor Xa assay and the description of which other serine proteases the compounds may inhibit. These do not affect the skilled medicinal chemist's consideration of the utility section and I would expect the skilled medicinal chemist to come to the same conclusions from this section of WO131 as from WO652....

[iii] *WO 03 049 681 A2*

8.1 After formulating my views of WO131 and WO652 I was provided with and asked to then consider the following documents:

8.1.1 Patent application WO 03 049 681 A2 entitled 'Synthesis of 4,5-Dihydro-Pyrazolo (3,4-C] Pyrid-2-0nes'('W0681') published on 19 June 2003 with a priority date of 10 December 2001; and

8.1.2 the Patent.

8.2 I was asked specifically to consider Example 53 of WO681 and the claims of the Patent. I have been told and understand that the Patent is in fact the granted patent that arises from WO652.

8.3 Example 53 of WO681 describes the compound 1-(4-Methoxy-phenyl)-7-oxo-6-[4-(2-oxo-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide (62)

[Image Not in Judgment Text]

8.4 Claim 1 of the Patent describes a compound which is represented by formula (1):

[Image Not in Judgment Text]

8.5 Having reviewed Example 53 of W0681 and Claim 1 of the Patent, I noticed that the structure as represented by formula (1) of Claim 1 of the Patent is the same structure as Compound 62 in Example53 ofW0681.

8.6 A side by-side comparison is set out in the table below. Although the structures appear to be slightly different the skilled medicinal chemist would understand that from a chemical standpoint, they are identical. Different nomenclature has been used but there is no ambiguity for the skilled medicinal chemist moving between the 1wo nomenclatures.

[Image Not in Judgment Text]"

Statement #2 of 2

"***GENERAL COMMENTS***

1.5 Dr Young's report refers to 'Apixaban' throughout instead of (where appropriate) "compound 18". This imbues compound 18 with an importance it does not warrant. Simply put: at the time under consideration, 2001, apixaban as a name was not known in the CGK. Thus, the skilled person would not know compound 18 was apixaban, BMS's drug. To refer to compound 18 as 'Apixaban' leads the reader to infer in their mind compound 18 is the drug, but this could not have been known at the time under consideration.

COMMON GENERAL KNOWLEDGE OF THE SKILLED MEDICINAL

CHEMIST

Overview of drug discovery and development process

1.6 At paragraph 18 Dr Young indicates 'In 2001, it would typically take a minimum of 2-3 years to go from the start of a project to the identification of a clinical candidate.' In my experience, the period from the project's commencement (at the target identification stage) to clinical candidate delivery often takes many more years than 2-3: the Hit-to-Lead phase could be 18 months to 2 years alone with Lead Optimisation taking up to another 3 years. However, some projects fail to deliver a clinical candidate at all.

1.7 I broadly agree with paragraph 19 of Dr Young's report in which he sets out the typical phases of a drug discovery process. Dr Young repeatedly refers to the need to test compounds at various stages of the development process (including for potency, selectivity and DMPK properties), and refers to the 'hope' of identifying a compound with suitable properties to be a potential therapeutic. Consistent with my first report, this indicates the importance of actually testing a compound in assays or animal models of interest before it progresses to further stages of drug discovery. The skilled person would agree there is no other way to identify a compound for progression without obtaining such data. Unless and until the skilled team has such data, the compound will not progress down the testing funnel, or to the next stage in the drug discovery process.

1.8 Dr. Young also indicates that, when identifying a promising compound, the skilled medicinal chemist would 'possibly' consider its selectivity. In my view, the skilled person would believe selectivity is essential, to avoid unwanted and deleterious side effects. As I explained in my first report, it was common (depending on the specifics of the project) in 2001 to set a threshold of 100-fold to 1000-fold selectivity over related enzymes (although a less exacting threshold, such as 10-fold selectivity, may be applied at an earlier stage of the discovery process).

1.9 Dr Young indicates that the drug discovery process progresses to the subsequent step at paragraph 19C only 'if a promising compound/class of compounds was identified'. I agree that the drug discovery team may not have found a compound of interest from their initial work. If this was the case, the skilled team would therefore need to repeat step 198 in order to generate a compound of interest.

The structure of factor Xa inhibitors

1.10 Paragraph 37 of Dr Young's report explains that certain known compounds with factor Xa inhibitory activity had a P1-core-P4 structure. I agree that this was a common structure of certain inhibitors, as explained in paragraph 6.47 of my first report. Thus, if the skilled medicinal chemist was provided with data showing that a compound of that structure did in fact bind, they would be able to rationalise after the fact and might explain its binding by reference to the P1-core-P4 structure. However, the skilled medicinal chemist would not be able to predict reliably whether any given compound with a P1-core-P4 structure would be able to bind to factor Xa (or begin to guess as to its potency or other characteristics, or binding mode).

1.11 Dr Young also states that the 'S4 binding pocket allowed for considerable variability". This is akin to the comment which I made at paragraph 6.47.4 of my first report that a 'great diversity' is seen in the P4 group in reported factor Xa inhibitors. However, similarly to the above, the observation that a variety of groups can be tolerated would not by itself enable the skilled

medicinal chemist to predict, when presented with a new compound and without binding data, whether it contains a substituent which would enable it to bind to the S4 pocket.

1.12 *At paragraph 38, footnote 3 Dr Young states that calculated pKa values were obtained using software from Advanced Chemistry Development (ACD/Labs) Software V11.02. I do not believe that this software would have been available in 2001. The skilled medicinal chemist would, at that time, be using algorithms that may have been less accurate than the version Dr Young is using. However, I agree that DX-9065A contains highly basic groups and that basicity would have been recognised by the skilled medicinal chemist.*

1.13 *At paragraph 39 of Dr. Young's report he states it was known in 2001 that the skilled person could move away from basic centres. I agree that strongly basic centres are in general terms associated with, for example, toxicity and poorer permeability and hence poor oral bioavailability. However, although the skilled person would want to move away from compounds containing strongly basic centres (particularly for orally administered drugs), such a modification will not guarantee the modified compound will present an improvement in, for example, toxicity or bioavailability, nor retain the former level of potency or selectivity.*

1.14 *At paragraph 40, Dr Young highlights the properties needed for obtaining 'clinically viable oral factor Xa inhibitors' as described by Zhu & Scarborough. Zhu & Scarborough describe this as preferably having a K; < 1 nM, which is consistent with what I have said in my first report that a potential therapeutic compound would need to display high potency in the low nanomolar or high picomolar range.*

1.15 *In paragraphs 41-43, Dr Young refers to 'Lipinski's rules' in connection with drug-like characteristics of a compound. In general, Lipinski's rules are guidelines and not hard and fast rules. The guidelines were used as a practical way of excluding compounds from the drug discovery process, particularly at the earlier stages. There are simply too many compounds which could be synthesised, and the skilled team required some method of reducing this pool down to a set that would actually be synthesised; Lipinski's guidelines provided one way to do this. This is reflected in the fact that different companies interpreted (and utilised) them to differing extents in directing their internal research. For an example from my own experience, Pfizer moved to a molecular weight limit of 450 Daltons.*

1.16 *These guidelines could be used to exclude compounds from synthesis at an early project stage, for example, as distinct from predicting which compounds will ultimately work. In other words, Lipinski's rules operate as a negative test to exclude compounds from further development rather than a positive one to suggest that a compound may have especial promise. Therefore, even if a compound did fulfill the Lipinski rules, the skilled medicinal chemist would not be able to predict that that compound would have suitable drug like properties.*

1.17 *Conversely, it was known in 2001 that certain clinical compounds did not fulfil the Lipinski criteria. I have provided two examples of marketed compounds that do not fit Lipinski's guidelines below. These examples reflect the fact that certain successful compounds did not adhere to the Lipinski rules which would, as a principle, have been known by the skilled medicinal chemist in 2001.*

1.18 *Lipitor® (also known by its generic name, atorvastatin), at one time the world's best-selling drug, was approved for market in 1996. Its structure is shown to the right. This drug is a statin medication used to prevent cardiovascular disease in those at high risk and to treat abnormal lipid levels. The drug has a molecular weight of 558.65 Daltons, and so does not*

fulfil the Lipinski criteria. The absolute bioavailability of the medication is about 14% but it is a successful drug.

1.19 *Singulair® (generic name montelukast) was approved in 1998 and its structure is shown to the right. This drug is a medication used in the maintenance treatment of asthma and so administered by inhalation. The drug has a molecular weight of 586.19 Daltons, a CLogP of 8.8 and an oral bioavailability of 63-73%.*

1.20 *At paragraph 45 Dr. Young states 'Techniques of combinatorial chemistry were ideally suited to the rapid exploration of the potential variations in binding modes and to explore novel motifs in a prospective manner.' Combinatorial chemistry is a technique used to synthesise large sets of molecules and thereby build a compound library of, perhaps, thousands of compounds. I would not consider combinatorial chemistry as well-suited to exploring variations in binding modes of binders to factor Xa. The approach would involve introducing each of the thousands of compounds to a preparation of factor Xa and, for those compounds which bind, attempting to produce a crystal which could be examined using x-ray crystallography. Analysis of the x- ray spectra would seek to determine the binding mode of the compound when bound to factor Xa. Repeating the process across many thousands of compounds would be impracticable and successful crystallisation would be a challenge for many compounds, so it is not 'ideally suited to rapid exploration' of binding modes. Further if molecular modelling were instigated (more suitable to higher throughput}, the skilled person would face the practical problem of whether to believe the result, given the propensity for obtaining, for example, reverse binding in factor Xa research.*

Paragraph 47: Example 1 DPC423:-

1.21 *From paragraph 46, Dr Young identifies certain specific compounds. I performed a similar exercise in paragraph 6.46 of my first report. In places, Dr Young and I have identified the same compounds as being particularly noteworthy. However, different medicinal chemists would likely identify different compounds as being of especial interest and there is variation between our respective compounds. Additionally, while Dr Young identifies literature papers which mention certain compounds, it is unclear how he identified those literature papers.*

1.22 *Dr Young and I both identified DPC423 as a compound of interest.*

Paragraph 48: Example 2 Lilly S1 methoxyphenyl:-

1.23 *Dr Young's second example is a member of a series designed by Eli Lilly. He identifies this compound as possessing a 4-methoxyphenyl group which is thought to be the S1 binding substituent. I did not identify this series nor this specific compound as being of especial interest. While some members of this Lilly series were reported to have low nanomolar KiS, that did not in my view set them out head and shoulders above the numerous other compounds and series being pursued in the field in 2001, many of which achieved similar levels of potency.*

1.24 *Dr Young identifies a number of papers in which his Example 2 or other members of the Lilly series are reported:*

1.24.1 *On pages 82-84, **Zhu 1999** sets out a range of example compounds from the Lilly series in Figures 35 - 38. These compounds display a variety of substituents including substituted aromatics, heteroaromatic systems, and fused rings. Zhu 1999 had obtained these compound structures from patents*

filed by Lilly and explains that the biological activities of the compounds were not disclosed. Accordingly, Zhu 1999 presents no data for any compounds in the Lilly series. While Zhu 1999 depicts the structure for over 20 compounds by Lilly, it does not show the member which Dr Young has selected as Example 2. Instead, it identifies the 4-chloro analogue with the piperidylpyridine substituent.

1.24.2 *On pages 1012-1013, **Betz** depicts 8 compounds from Lilly, including 5 compounds from this series. Again, none of these is the Example 2 compound which Dr Young has selected. Instead examples 37 and 38 in the Betz paper both contain the piperidylpyridine substituent with a 4-chloroaryl substituent. Like in Zhu 1999, no biological data are given for any members of the series.*

1.24.3 *On page 113, **Rai** identifies a selection of compounds from various companies. One of these is a Lilly compound, though not the same as that identified by Dr Young.*

1.24.4 *Pages 1518-1519 of **Ries** depict the structure of a handful of Lilly compounds. Certain of these are substituted with the 4-methoxyphenyl substituent akin to Dr Young's Example 2; others are substituted with chloro-substituted phenyl groups or bear other substituents. In this regard, Ries comments that "substitution of the right 4-methoxyphenyl fragment in [compound] 54 by the 3-amidinophenylgroup furnished highly active amidine 59", which had a Ki of 2 nM and was superior in the rabbit AV shunt model. Ries thus suggests moving away from the 4-methoxyphenyl substituent in order to improve potency, albeit back to a more basic substituent.*

1.24.5 ***Zhu (2000)** highlights compound 69a (on page 94) from the Lilly series and reports that it demonstrates biological activity (such as K; 10nM and activity in the rabbit arterio-venous thrombosis model). However, compound 69a possesses the 4- chlorophenyl group (not the 4-methoxyphenyl group of Dr Young's Example 2), again indicating replacement groups to 4-methoxyphenyl group can be advantageous and were seen as key compounds by literature reviewers. Compound 69a also contains the piperidylpyridine substituent as shown in Example 2, but with a different linker in the compound scaffold.*

1.24.6 *On page 167, **Maignan** identifies three compounds from the Lilly series of which one (compound 24) is Dr Young's Example 2. The authors explain that the analogous chlorophenyl group could replace the methoxyphenyl, leading to a 6-fold improvement in potency, whilst maintaining in vivo efficacy. Thus, there is nothing special about the 4-methoxyphenyl group as an S1 substituent and Maignan highlights better replacements.*

1.25 *The above discussion is consistent with my overview that, while the Lilly series contained members which had low K; potencies, they did not stand apart from the field in 2001. There was no indication of a clinical trial nor advanced animal testing across the width of the series. Further, the literature highlights there is no direction in favour of the 4-methoxyphenyl substituent as the preferred substituent. Instead, various reports suggested moving away from the 4-methoxyphenyl substituent based on reported data. Moreover, aside from the Maignan paper, I did not find Example 2 specifically identified in any other of Dr Young's cited papers. It is therefore difficult to conclude Example 2 is of importance, over and above a range of analogues from the pool of inhibitors presented.*

Paragraph 49: Example 3 Fidexaban:-

1.26 *Dr Young refers to Example 3 as 'fidexabf}n', though I did not see this name used in relation to this compound in any of the papers which Dr Young cites.*

1.27 I agree with Dr Young that this compound is dibasic and the industry was at this time moving to less basic or neutral compounds. However, I note that this compound has a Cl number (indicating that it was undergoing testing in clinical studies) and was identified in Ries and Zhu 2000 as a clinical candidate. If it had been pointed out to the skilled medicinal chemist that a compound was in clinical trials, this knowledge would have elevated their interest in the compound.

Paragraph 50: Example 4: Zeneca:-

1.28 Dr Young cites this Zeneca compound as being of importance. This compound has a K; of 3 nM, which is promising but does not set it apart from the lit_erature in particular. Dr Young highlights the problem of determining the binding mode of compounds such as these; reverse binding occurs making a prediction of binding mode imprecise. This would reduce the skilled person's certainty as to how this compound binds. Additionally, while Dr Young cites the example in Figure 10 as a compound with reduced basicity, this compound, with a calculated pKa of 10.88, is still highly basic.

1.29 Dr Young identifies some literature papers concerning this molecule:

*1.29.1 **AI-Obeidi** provides activity data against factor Xa, thrombin, prothrombin and thromboplastin followed by the statement that the compound "was also active in vivo at 5 mg/kg". The paper does not appear to indicate which animal species the compound was tested in.*

*1.29.2 The **Ries** review cited by Dr Young identifies this compound as compound 38 amongst various other compounds from the same series. It is described as a 'typical' example and further disclosed patents seek to replace functionality contained within this compound. There is nothing to distinguish this example from many others in the literature.*

*1.29.3 **Zhu 2000** provides the structure of this Zeneca compound on page 95 as example 72a. The authors indicate that the piperazine ring can be substituted and retain activity, thus there is nothing unusual about the example in Dr Young's Example 3.*

*1.29.4 **Zhu 1999** on page 81 cites Example 4 as compound 83. It explains that this compound is a representative example of the Zeneca series with nothing to distinguish itself from its analogues.*

*1.29.5 **Betz** presents 4 compounds from Zeneca but none of these is the same as Example 4, nor is any biological data given for the series.*

*1.29.6 On page 113 of **Rai,** one Zeneca compound is identified, and a measure of activity is given. However, the compound in Rai is not the same compound as Example 4 in Dr Young's report.*

Paragraph 51: Examples 5 and 6

1.30 Both Dr Young and I have identified some RPR compounds and have both identified RPR120844 (Example 6 in Dr Young's report), and each of us has identified one different compound from the other.

*1.31 Dr Young additionally cites as Example 5 the compound RPR200443, a compound which displays a weakly basic centre (pKa 8.13) and a member of a well-developed series of compounds. **Zhu 2000** states on page 98 that this compound, identified as example 88 in this paper, has a Ki of 4 nM. **Pauls** on page 97 highlights the good selectivity for Example 5 (compound 131 in Zhu (2000)) at> 1000-fold against relevant serine proteases.*

1.32 Summarising these compounds of interest at paragraph 53, Dr Young states" Thus tens, even hundreds, of compounds were quickly synthesised,

purified, and prepared for testing, enabling the identification of new chemical structures with unique binding modes..." but as already acknowledged in the literature, confirming binding modes was problematic due to the difficulty at this time in obtaining x-ray protein/liganded structures and the fact that binding modes would "reverse" and thus not be as predicted.

THE APPLICATION

1.33 *At paragraph 56 Dr Young states that '...the skilled medicinal chemist would recognise that it is focussed on a particular class of compounds .'. I do not agree that the notional, uninventive skilled medicinal chemist would recognise that the Markush in the Application is 'focussed' on lactams. Dr Young arrives at this conclusion following a carefully-worked and hypothetical analysis he is projecting onto the skilled person, in suggesting they could immediately recognise, from a broad formula (P4-P-M-M4), the importance of lactam substituents. It is more accurate to say that lactams are "buried within" the Markush formulae of the Application.*

1.34 *Dr Young then itemises the various embodiments in WO652. In relation to embodiment 8, he states at paragraph 64 that the '..skilled medicinal chemist could readily analyse the structures of the compounds based on their chemical names'. He appears to envisage converting the names of the 74 compounds listed in embodiment 8 into structures. While this exercise would be mechanical in requiring the close application of rules to convert a name into a structure, it would entail considerable time to perform.*

1.35 *He continues in paragraph 64 to state that the '..skilled medicinal chemist would quickly recognise that the compounds listed in embodiment 8 are pyrazolopiperidones of the type shown in embodiment 7'. I disagree that the comparison would be quick for the reason given above, namely that the skilled person would need to manually convert a chemical name into a structure for a large number of compounds. Identifying and drawing out the structures would take hours. Furthermore, Dr Young should not be understood as saying that all the compounds of embodiment 8 fall within the Markush formula defined by embodiment 7. As embodiment 7 shows on page 68, lines 5-9 of WO652, the permitted substituents at A-B are 4-(2-oxo-1-piperidinyl)phenyl- (as shown on the left in the Application) and 4-(2-oxo-1(2H)- pyridinly)phenyl (as shown on the right) according to the notation used in WO652. Certain of the compounds in embodiment 8 do not meet this requirement, such as those identified on page 69, line 6-8, page 69, line 14-16, and page 69, line 18-20 of WO652.*

1.36 *In paragraph 65 and Figure 17, Dr Young presents the conclusions from a frequency of use analysis. While he does not explain his method for preparing this analysis, it appears that he has converted the names of compounds into structures, discarded certain of the structures which appear to differ from the rest, and then performed a counting exercise to identify the number of times a particular substituent is used. This would have been an enormous amount of work.*

1.37 *In paragraph 66, Dr Young states that 'Based on the repeated use of this core and an analysis of the frequency of the substituents used (such as that shown above), a skilled medicinal chemist would recognise the preferred substituents and where changes were focussed to secure potency and/or optimal pharmacological and physicochemical properties'. However, this analysis does not teach the skilled medicinal chemist anything about the*

potency or other properties of the compounds. As no data are provided for any of the individual compounds, it is no better than guesswork to conduct this review.

1.38 *At paragraph 67 Dr Young states "As with embodiments 1 to 8 described above, each of embodiments 9 to 15 comprises a Jactam substituent, but whereas the later embodiments in the series of embodiments 1 to 8 are focussed on compounds with a fused bicyclic core, embodiments 9 to 15 are focussed on compounds with a monocyclic core." However, I believe 'later' here is a mistake and this should be "earlier'.*

1.39 *At paragraph 69 Dr Young states that 'The skilled person would understand this to mean that the inventors had tested some of the synthesised compounds and found them to be effective factor Xa inhibitors.' It is not clear to me what Dr Young means by an 'effective' factor Xa inhibitor. As I explained in my first report, the skilled team would be looking for potency in the low nanomolar or high picomolar range in addition to 1OD-fold to 1000-fold selectivity over related serine proteases. The 10 μM figure is a typical cut-off mark at the start of the project, and does not describe a compound which might be an effective therapeutic. In any event, it is clear from WO652 that there is no actual biological (e.g., Ki data) assigned to any compound, so it is clearly not possible to make the deduction Dr Young claims.*

1.40 *In paragraphs 70 to 72, Dr Young presents the results of a similar frequency of use analysis. The same reasoning as above in my response to Paragraph 65 applies. Frequency does not translate to a definitive way to identify important substituents. Thus, when Dr Young claims 'In the P1 position, 50/110 of the substituents are methoxyphenyl, with the balance of the alternative substituents being plausible alternatives to methoxyphenyl ...', in the absence of data, a frequency of use analysis provides no technical basis for thinking any of compounds achieved any particular property, such as a desirable level of potency.*

1.41 *In paragraph 73, Dr Young states that "The skilled medicinal chemist would note that the compound of example 18 (which is apixaban) was prepared on a much greater scale than any of the other synthesised examples". He goes on in paragraph 74 to state that the 'large quantity of the compound of example 18 (apixaban) that was prepared would indicate to the skilled medicinal chemist that example 18 (apixaban) was of particular interest to the inventors...'. Dr Young intends the reader to understand that Compound 18 is clearly the clinical candidate and the only compound of real interest.*

1.42 *I do not agree that the skilled medicinal chemist would draw this conclusion. WO652 discloses no biological data associated with any compound. However, data and biological activity are the indicators of interest and synthesis scale does not inform the skilled medicinal chemist about any of example 18's properties, including those which might make it suitable as a therapeutic factor Xa inhibitor.*

1.43 *The synthesised quantity does not indicate that example 18 was 'of particular interest to the inventors' either, as Dr Young states in paragraph 74. The syntheses of the exemplified compounds would likely have been conducted by numerous different medicinal or synthetic chemists working within a team. Different chemists may synthesise different amounts of compounds, or follow a different purification procedure, for example. The synthesised quantity may have been different if example 18 was synthesised by a different chemist. Additionally, a compound may be made in a larger quantity for other reasons such as being an intermediate to synthesise other derivatives. Further, as I explained in paragraph 7.21 of my first report, WO652 states that "[s]ome*

compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin". Therefore, even if example 18 was 'of particular interest', that may instead have been for its thrombin inhibitory properties.

1.44 *Dr Young states that 3.07g of example 18 was synthesised and that a second recrystallisation was carried out. While the experimental in WO652 for Compound 18 is poorly written, I do not think this is an accurate portrayal of the steps which were undertaken. First, a recrystallisation was not undertaken. Rather, a first crystallisation (so not a recrystallisation) is performed on the evaporated material residue from the chromatography procedure, from which 2.5g of the compound was obtained. Then, a second crop of crystals obtained from the mother liquor (i.e., evaporating the eluent) and this material is crystallised from a different solvent (isopropylalcohol). This provided a second crop of 0.57g. Thus, the 2.5g and 0.57g crops were purified separately from the chromatography step using different solvents, and neither involved a recrystallisation.*

1.45 *There is no indication of the purity profiles from each batch, nor whether the proton NMR spectra obtained refers to one batch or the other, or a combination. Generally, a medicinal chemist would not combine batches of compound without first determining their respective purity profiles and determining they are the same compound. Different batches with different impurity profiles would not necessarily progress along the screening cascade for fear of giving false results. Conceivably, the chemist retained only 0.5g of material, if this was the purer batch having found that the former, larger batch may not be pure enough. Given that the two batches were crystallised from different solvents, it is very possible that they achieved different purities. Alternatively, different chemists could apply their own "style" for purification, for example. Some preferred a flash column, while others focussed upon crystallisation first. It is conceivable that this could explain why a second crop of crystals was obtained, merely being down to the individual chemist's modus operandi.*

1.46 *Further, aside from the proton NMR, no other data characterising the example 18 compound are provided. By contrast, there are a number of other compounds produced in hundreds of milligram scale for which further data that characterise the compound have been provided. For instance, example 3 on page 194 was synthesised in a 410 mg quantity and data from a low-resolution mass spectrometry in addition to proton NMR are provided; and example 14 on page 210 was synthesised in 150 mg quantity and characterised by Liquid Chromatography Mass Spectrometry and NMR.*

1.47 *At paragraph 77 Dr Young states that '...it would have been plausible to the skilled person that apixaban was an effective (and improved, cf. paragraph 99) factor Xa inhibitor. I consider that this would have been plausible ...'. As I have explained, this conclusion would not be reached by the skilled medicinal chemist because there are no data to support the contention that compound 18 was apixaban, nor is there any biological data to suggest this compound is effective as a factor Xa inhibitor.*

1.48 *Dr Young then provides various reasons to support his conclusion in paragraph 77. I have been asked to discuss these in turn. In relation to 77A, as I have explained in paragraph 1.10 above, that a compound that has a P1-core-P4 structure would not enable the skilled medicinal chemist to predict reliably whether it would bind to factor Xa (nor with what potency or other relevant characteristics).*

1.49 *In paragraph 77B, Dr Young refers to the Lilly compound he identified as Example 2 in connection with the methoxyphenyl substituent. As I have explained above, I do not believe that this compound would have formed part*

of the common general knowledge. Further, both Ries and Maignan identify analogues to the 4-methoxyphenyl substituent which provided a more favourable potency. In any event, even if the skilled medicinal chemist had in mind the specific compound which Dr Young identifies as Example 2, they would not be able to predict reliably that any compound with that substituent would offer suitable binding to factor Xa.

1.50 In paragraph 77C, Dr Young draws a comparison between DP423 and example 18. I have reproduced below a comparison of the structure of DPC423 next to example 18 (apixaban).

1.51 As is visible from the structures depicted, DPC423 is the left-hand structure below and example 18 is the right-hand structure below.'

[Diagram not included in judgment]

1.52 While the structures are presented in the same orientation, as I explained in my first report (paragraphs 6.47.3 and 6.47.6), it was understood that compounds might bind in the 'reverse mode' to that which may be expected based on similar compounds. Therefore, undertaking a point-by-point comparison between DPC423 and example 18 might not inform the skilled medicinal chemist correctly regarding compound design given the known occurrence of 'flipping'.

1.53 On the lower left-hand side of each molecule, DPC423 contains a benzylamine substituent whereas example 18 has a methoxyphenyl group. These substituents have different shapes and different electronics. As is shown, the phenyl group is substituted at the meta position in DPC423 but in the para position in example 18. The primary amine in DPC423 can act as a hydrogen-bond donor and acceptor whereas the oxygen atom in example 18 could act as a hydrogen-bond acceptor only. Further, the p-orbital on the oxygen is conjugated. with the aromatic system in example 18, thus donating electron density to the phenyl group; and this does not occur in DPC423.

1.54 Second, DPC423 bears a trifluoromethyl group which is replaced with a carboxamide in example 18. The trifluoro group is likely to introduce more lipophilicity into DPC423, whereas the carboxamide may make backbone interactions with factor Xa.

1.55 Third, on the right-hand side, the sulphone in DPC423 is replaced with a lactam in example 18. The sulphone is an aromatic substituent which is planar and capable of TT-stacking interactions which would be missing from example 18.

1.56 Fourth, I agree with Dr Young that example 18 contains a cyclised core as compared with DCP423 and that this will rigidify the molecule. That cyclisation will freeze out the rotational degrees of freedom which are possible in DPC423, which may lead to an increase in potency or could entirely ablate potency depending on whether or not the P1 and P4 binders were held in appropriate positions or it could cause the binding to 'flip', thus making predictions of potency difficult. The skilled medicinal chemist would not know whether activity had been improved or removed without testing and analysing the data. I therefore disagree with Dr Young's statement that rigidification was 'likely to increase affinity'.

1.57 As noted above, each of the substituents on DPC423 is changed and the core is cyclised to arrive at example 18. There are 6 major changes, including cyclisation, which makes the possibility of predicting potency very difficult. Note in this report and my first report that single structural changes can cause large changes in potency and selectivity (see paragraph 1.60 below), as well as, in principle, other changes such as ADME properties and the result of these multiple changes on moving from DPC423 to apixaban would

mean that predicting the potency would be very difficult.

1.58 *At paragraph 77D Dr Young states '..the skilled person would know that the S4 binding pocket allowed for considerable variability and, having been presented with it, would consider it plausible that the lactam substituent of apixaban would bind in the S4 pocket.' It cannot be stated that the lactam would bind to the S4 binding pocket, rather that it is possible that it could bind here. The skilled person would not know a priori that it would bind, as data would need to be obtained to show this, of which there is none presented in the Application.*

1.59 *In paragraph 77E, Dr Young revisits the frequency of use analysis which I have responded to above. Additionally, he states that there are 32 compounds in WO652 which only have a single point change from example 18. Dr Young did not identify which compounds these are, and I have not sought to do so.*

1.60 *However, it was well appreciated that a single-point change could have a large impact in terms of potency, selectivity or other properties. I have set out at* ***Appendix 1*** *a table comparing compounds with single-point changes and identifying the fold-difference in activity which that structure change causes.*

1.61 *Further, Dr. Young fails to indicate that, the CF3 groups (R3 substituent on Figures 17 and 18, paragraph 65 for Figure 17 and paragraph 70 for Figure 18 of Dr Young's report) has a frequency count of 20/74 (Figure 17) and 23/110 (Figure 18), whereas the carboxamide substituent appears in only 13/74 (Figure 17) 19/110 (Figure 18) examples. The CF3 substituent is present in DPC423 but a carboxamide is used in example 18.*

1.62 *At paragraph 77F Dr Young refers to the synthesised amount of example 18 which I have responded to above. The determination of which compounds may be of interest to the skilled person is, ultimately, guesswork by Dr. Young. Compounds in WO652 could be thrombin inhibitors and their synthesis subject to individual chemist's synthesis variations, As discussed above, only 0.5g of compound 18 may have been kept and progressed due to purity issues.*

W0131

1.63 *At paragraph 78 Dr Young states 'I consider that the skilled person would find it plausible that apixaban was an effective (and improved) factor Xa inhibitor such that they would want to make and test apixaban." However, the skilled person would not identify apixaban as a compound of interest from WO652 as there is no supporting data. Dr Young goes on to write "If the skilled person were to do so, they would find that not only was apixaban an effective factor Xa inhibitor, but that it also was an improved factor Xa inhibitor and had the other properties that were sought after in an efficacious factor Xa inhibitor'. As mentioned above, this statement is speculation and cannot be substantiated by any supporting data in WO652.*

1.64 *At paragraph 79 Dr Young states '... in WO 131 the text is the same as in the Application that I discuss above...' but it is not the same, merely similar with some changes.*

1.65 *At paragraph 83 Dr Young states 'However, there is a much greater diversity in the structure of the examples of WO'131 than can be seen in the examples of the Application.' Yet, having regard to the scopes of both patents, the BMS application, W0652 contains a larger scope.*

1.66 *At paragraph 86 Dr Young makes a point on frequency of substituent appearance. However, this is not substantiated for the same reasons I make in paragraphs 1.36 and 1.37 above.*

1.67 *At paragraph 88 Dr Young makes the point that the skilled person would recognize '...that most of the examples of WO 131 would be effective factor Xa inhibitors, such as Example 67, which has a similar structure to DPC423.'*

However, given that W0131 contains no biological data, the skilled person could not be expected to know that most examples were effective factor Xa inhibitors.

1.68 *At paragraph 93 Dr Young again performs a frequency of use analysis in this paragraph that would teach toward R3 being trifluoromethyl. For the same reason as above, namely the lack of data, the skilled medicinal chemist simply could not form the conclusions which Dr Young advances.*

1.69 *At paragraph 95 Dr Young states that W0131 has a higher distribution of molecular weight compounds compared to W0652. For the reasons highlighted In paragraph 1.15 above, there is an over-reliance placed on Lipinski's guidelines as if they were rules or had the capacity to predict which compounds will have suitable drug-like properties. The skilled medicinal chemist would therefore not be able to infer that W0652 contains druglike compounds, whereas W0131 does not. T e calculated values from Lipinski's guidelines does not confirm the presence of a compound with suitable drug-like properties.*

1.70 *At paragraph 96 Dr Young makes a similar point to that in paragraph 95, this time concerning lipophilicity. Again, this analysis does not enable the skilled medicinal chemist to infer whether W0131 contains drug-like compounds. Reference to the average CLogP of the whole patent versus a single compound, apixaban, is not valid in that it does not exclude the presence of a drug in W0131 or other compounds in W0131 with a similar (or lower) lipophilicity to apixaban. Further, Dr Young points out that W0131 contains compounds with a similar CLogP to apixaban, indicating that apixaban is not an improvement over the body of compounds in W0131. Dr Young's argument rests on calculated (not real) properties, with reference to guidelines that do not encompass all drugs.*

1.71 *At paragraph 98 Dr Young states 'In comparing the Application and WO 131, the skilled person would also observe that, unlike apixaban, none of the exemplified compounds in WO131 had been synthesised in a gram scale or on a scale that suggests they were scaled up for comprehensive testing...'. I have explained above the numerous reasons that exist for variation in synthesised amount. Further, the statement that the compounds were scaled up for comprehensive testing cannot be substantiated because the skilled medicinal chemist would not know whether the synthesised quantity was sufficient to provide substantial biological data. The amount of compound needed to perform biological tests would depend on at least the potency of the compound. Further, footnote 10 in Dr Young's report simply highlights that other examples were prepared on a similar scale to compound 18 in W0652. It is not as though the difference is between a few hundred milligrams and compound 18 being prepared on, say, a 1kg scale.*"

APPENDIX 4

Abridged Written Evidence of Dr Gallagher

Statement #1 of 2[18]

"*SKILLED PERSON/SKILLED TEAM*

5.1 *The concept of the 'skilled person or team' has been explained to me by Teva's solicitors, Pinsent Masons (Ireland), as a hypothetical construct which has been developed to help the court read and understand patents essentially from the point of view of a person with an interest in reading the patent at the time it was written. My understanding of the concept of the skilled person, or by extension the skilled team, as explained to me is that the individual is a person skilled in the art to whom a patent is addressed and who would have a practical interest in the subject matter of the patent. The skilled person (which can be a skilled team) is uninventive but has the common general knowledge in the relevant field.*

5.2 *I have reviewed W0131 and W0652 with a view to considering who should be regarded as the skilled team. They are very similar documents and I think they are both addressed to the same notional skilled team, which is a team interested in developing FXa inhibitors which could potentially be useful as anticoagulants/antithrombotics.*

5.3 *There were a number of criteria that were commonly considered to be the properties that those working in the field of discovery of antithrombotic agents would be looking for in potential lead compounds (i.e., compounds that might be good enough to advance to clinical evaluation). The criteria were that the compound should:-*

5.3.1 *be specific for a particular physiological target (in this case FXa);*

5.3.2 *inhibit thrombosis;*

5.3.3 *not affect hemostasis to such an extent that bleeding problems would arise;*

5.3.4 *have a half-life appropriate for a particular clinical indication;*

5.3.5 *be absorbed after oral administration; and*

5.3.6 *have a large therapeutic range (i.e., is effective and safe across a relatively wide dose span).*

5.4 *The job of a drug discovery/development team was to synthesize chemical candidates, conduct in vitro and ex vivo assays to measure their activity against a target enzyme (such as FXa) and perform appropriate in vivo studies in animal models to demonstrate biological utility. Therefore, real-world drug development teams typically included skilled individuals representing virtually every department in the organization: Chemistry, Pharmacology, Pharmacokinetics, Toxicology, Translational Medicine, Clinical Operations, Clinical, Regulatory, and Marketing.*

5.5 *Having looked at W0131 and W0652 I think they were primarily directed at a medicinal chemist and pharmacologist ('Skilled Person' or 'skilled pharmacologist') and these are the disciplines that I think make up the skilled team ('Skilled Team'). I do not think that there is information or data in W0131 and W0652 which is directed to the later elements of the*

[18] The texts of the papers appended by Dr Gallagher to his statement are not included here. Also, diagrams shown in the original version are not shown in this abridged version.

development process such as toxicology, pharmacokinetics, clinical studies, regulatory interactions, or marketing.

5.6 *I have been asked to prepare this report from the perspective of a pharmacologist working as part of the Skilled Team (the skilled pharmacologist). The skilled pharmacologist would usually have a PhD in pharmacology, physiology or a related subject and several years of experience-in academic and/or industrial research. The pharmacologists developing FXa inhibitors would have been familiar with the common general knowledge that existed in the field of hemostasis, thrombosis and antithrombotics.*

5.7 *Although I speak as the skilled pharmacologist, I worked closely with medicinal chemists in teams developing FXa inhibitors and I think it is relevant to describe the role of medicinal chemists from my first hand experience. Medicinal chemists were responsible for identification/design and synthesis of compounds. These would be provided to the skilled pharmacologist for testing in vitro and in vivo (in animals). Medicinal chemists working with pharmacologists will try to establish the structure activity relationship (SAR) for a chemical structure by adding different substituents (making small chemical structural changes), then pharmacologists evaluate the effect of the changes on biological activity. Based on an assessment of how the structural changes alter the biological properties of the compounds, the medicinal chemist makes further incremental modifications to try to improve desirable properties such as potency and selectivity. This is an iterative process with the goal of finding potent, selective, biologically active compounds with the necessary physicochemical and other properties to take forward into clinical development. It is a painstaking and time-consuming process with no guarantee of success.*

5.8 *The skilled pharmacologist was responsible for testing the activity of candidate compounds in a series of tests. The first, essentially "door opener" test, when developing an enzyme inhibitor is an in vitro assay to see if the compound inhibits the enzyme of interest (at relevant concentrations). These types of assays were conducted under non-physiologic conditions (ie, in a non-blood solution, with purified enzymes, and using non-physiologic substrates) to provide fairly rapid and convenient assessments of inhibitory activity.*

5.9 *The skilled pharmacologist would also carry out tests on other related enzymes to see whether the compounds were specific for the target of interest, in this case FXa. This requires that the compound does not inhibit to any significant degree the activity of the mass of other structurally related enzymes and receptors that could negatively impact activity in vivo and safety.*

5.10 *If compounds were sufficiently potent and selective in the above assays, the next step would be to see if the compounds have an effect on clotting. The skilled pharmacologist would perform clotting assays in systems that more closely approximated the actual physiologic circumstances in which an inhibitor would be used, usually plasma derived from whole blood or whole blood. A number of standardized tests were available at this time to see if a compound had antithrombotic activity (ie, an ability to slow down the rate of clotting) in plasma or blood in a test tube or other appropriate container.*

5.11 *The next steps for compounds which had been shown to have an antithrombotic effect in vitro would be animal experiments to evaluate whether those compounds worked in vivo.*

5.12 *The skilled pharmacologist was usually responsible for identification of a*

'lead compound' (a candidate compound good enough to justify substantial resource investment and advancement to clinical studies in human subjects) which required establishing its potency, selectivity, activity in clotting assays and utility in animal models of thrombosis.

5.13 *Since an antithrombotic agent will interfere with blood clotting, the balancing act is to reduce blood clotting in the right place, at the right time, and in the right amount, all without causing serious side effects such as excessive bleeding. The disciplines of Pharmacokinetics, Safety, Pharmacology and Toxicology, accordingly, had to work together closely before a decision could be made to advance a lead compound into clinical studies involving human subjects. However as stated above, I do not think there is any information in W0131 and W0652 which would be of interest to those involved in these later stages of the drug discovery and development process.*

COMMON GENERAL KNOWLEDGE

6.1 *I have been asked to describe the common general knowledge of the skilled pharmacologist in the field of thrombosis, treatment of thromboembolic disorders and the development of inhibitors of FXa at the Relevant Date.*

6.2 *My understanding of the concept of common general knowledge and as explained to me is that it represents the information that is generally known to the bulk of people working in a particular field and generally accepted by them as a reliable basis for further work at the relevant time. It encompasses material that the Skilled Person can call to mind. Furthermore, I understand that common general knowledge is typically represented by information in textbooks or published review articles, which were widely read or consulted at the relevant time and is not limited to the material that the Skilled Person has memorized but also includes some information which is known to exist by the Skilled Person and would be referred to by them as a matter of course ("CGK"). In terms of drug development, for example, the information would be that which is generally accepted by the bulk of people as a reliable basis for determining if a project should or should not continue to move forward through the stages of drug development.*

6.3 *Before elaborating on some of the relevant concepts, it might be useful to explain at a high level some important terms that appear frequently.*

6.4 *Hemostasis is a process to stop bleeding. Blood is supposed to stay inside blood vessels and constantly move from the heart to the capillaries (where the exchange processes occur that keep cells – and, therefore, you and me – alive) and back again. Hemostasis refers to the processes that stop loss of blood (hemorrhage, the opposite of hemostasis) from a damaged blood vessel.*

6.5 *Blood clotting also known as coagulation is the mechanism by which higher organisms arrest blood loss following vascular injury. It is the process by which blood changes from a liquid to a gel, forming a blood clot. It potentially results ln hemostasis (cessation of blood loss from a damaged blood vessel followed by repair of the vessel). The mechanism of coagulation involves activation, adhesion, and aggregation of platelets that can form a 'plug' rapidly at the site of injury (identified as primary hemostasis). Simultaneously, coagulation factors in the blood are activated in a 'cascade' that results in formation and deposition of insoluble fibrin strands which strengthen the platelet plug (a process identified as secondary hemostasis). Another series of factors make up the fibrinolytic system, which later breaks down and removes the fibrin clot once it is no longer needed. The complex and dynamic processes of hemostasis and fibrinolysis are carefully balanced*

under normal conditions. Abnormalities in any of the hemostatic or fibrinolytic components upset the balance, leading to excessive bleeding or thrombosis.

6.6 *Thrombosis is the pathological development of blood clots. When coagulation occurs in the wrong place or at the wrong time, the clot is pathological and is identified as a 'thrombus'. Such clots, for example, may form in veins (potentially becoming a deep venous thrombosis or DVT). If the clots break free and become mobile (able to travel in the blood), they become an embolus that can lodge elsewhere in the circulatory system (such as the lungs; hence the term pulmonary embolus). Blood clots can also develop in the left atrium of the heart (often in patients with atrial fibrillation) which, if embolized, can lodge in arteries supplying the brain (causing an ischemic stroke). Thrombosis can also occur in coronary, cerebral and peripheral (usually in the legs} arteries that are narrowed and have altered internal lining of the blood vessel due to atherosclerosis. Thromboembolic diseases are the leading causes of morbidity and mortality in most industrialized societies.*

6.7 *Antithrombotic is the broad term for any medication that decreases clots in the body (by dissolving already formed clots or preventing clot formation). The types of antithrombotics are:*

6.7.1 *Anticoagulants: These types of medications prevent formation of a clot. They do not dissolve a clot already formed but help to prevent further propagation of a clot. They are often called 'blood thinners' although they do not actually 'thin' the blood, rather they make it more difficult for blood to form blood clots. Examples of anticoagulants available in the late 1990s/early-2000s were warfarin, heparin, and low molecular weight heparin; all of which were used, for example, in patients with deep venous thrombosis.*

6.7.2 *Antiplatelet agents: These agents prevent platelet aggregation (formation of a platelet 'plug"). In this timeframe the main anti-platelet drug was aspirin.*

6.7.3 *Thrombolytics (sometimes also called fibrinolytics): These agents decrease clot size and help dissolve clots already fanned. In this timeframe, there was a lot of clinical research underway with thrombolytics to evaluate their utility in patients with myocardial infarction or ischemic strokes.*

6.8 *Enzymes and enzyme inhibition: Enzymes are proteins that play many key roles to maintain homeostasis, energy metabolism, and, apropos of this report, control the coagulation cascade. Enzymes are proteins. Like all proteins they are made up of long chains of amino acids transcribed from DNA or RNA templates. They catalyze (or accelerate} the rates of chemical reactions by lowering the activation energy needed to carry out a reaction. There are several different kinds of enzymes and each type works on one particular or a set of particular substrates or reactions. Their specificity comes from the fact that the shape of the enzyme will determine its overall function and this means an enzyme is usually tailored to work on one substrate.*

6.9 *All enzymes have special folds in their three dimensional structure designed to fit a specific substrate, called an active site. Once a substrate is attached to the active site, a cofactor is normally needed in another receptor or fold of the enzyme for it to perform its function. Cofactors (such as vitamins, co-enzymes, ions such as Ca2+) may join the enzyme to form a complex that can enhance its performance.*

6.10 *There are three types of enzymatic inhibition: (1) Competitive inhibition occurs when a molecule similar in structure to the substrate binds to the active site thereby preventing the enzyme from performing its function. (2) Noncompetitive inhibition occurs when an inhibitor blnds to an area other*

than the active site of an enzyme (which may change the shape of the enzyme and/or block the active site). (3) Allosteric inhibition involves the addition of an activator molecule to its allosteric site (the site where activators or inhibitors bind to). Allosteric regulators include hormones, neurotransmitters, or other types of cell signalling molecules.

6.11 *For the purposes of this report, the two relevant types of inhibitors are competitive inhibitors (which compete with the natural substrate of the enzyme to occupy the active site) and noncompetitive inhibitors (which bind someplace on the enzyme other than the active site).*

6.12 *Serine proteases are a large class of enzymes that cleave peptide bonds in proteins. Serine serves as the nucleophilic amino acid in the enzyme's active site, hence the name. Serine proteases are found ubiquitously in both eukaryotes and prokaryotes. Many of the clotting factors, including Factor X, are serine proteases. Likewise, plasmin, the enzyme that helps dissolve fibrin to break down clots, is a serine protease. Other examples include chymotrypsin, trypsin, and elastase which are important pancreatic digestive enzymes and acrosomal protease which is an important element in sperm penetration of ova. Since serine proteases have certain structural elements in common across the whole class of these proteins, identifying an inhibitor specific for one serine protease (such as FXa) but not for other serine proteases is an important challenge to overcome to minimize the likelihood of side effects. When the term selectivity is used by pharmacologists in this context, it refers to the goal of identifying inhibitors that are selective for one target enzyme and not for other enzymes. This is evaluated by comparing the Ki or IC50 values for an inhibitor against the target enzyme (such as FXa) and against related enzymes (such as thrombin and trypsin). Ideally, for example, to demonstrate selectivity, the Ki against the target is low (indicating high potency) and the Ki against the related enzymes is several orders of magnitude higher (lndirating [sic – indicating?] low potency). This is the sort of information that would provide confidence that a low dose of the inhibitor could effectively inhibit activity of the target enzyme but not nontarget enzymes.*

6.13 *Coagulation Cascade is the term used to describe the series of reactions in which proteins in the blood (the 'clotting factors') are activated in a sequential manner that culminates in formation of fibrin clots in which red blood cells and other blood elements are trapped.*

6.14 *Clotting factors are the naturally occurring proteins which are present circulating in the blood which, once activated, result in clot formation. Because it is critical that clotting does not take place unless it is necessary to repair an injured blood vessel, most clotting factors are present ln the body in an inactive form. Upon a trigger event such as vascular injury, the clotting factors are sequentially activated, converting the inactive precursor protein into an active enzyme that can activate the next factor in the cascade. An important feature of the coagulation cascade is the amplification that occurs at each step. Clotting factors are usually indicated by Roman numerals and in the activated state have the suffix a. For example, FX is the inactive precursor of the active enzyme, FXa.*

6.15 *As shown in Figure 1 below, the initial stages of the coagulation cascade can be divided into two pathways, the intrinsic and extrinsic which converge on a common pathway to generate FXa which in turn activates prothrombin to thrombin which catalyzes the last step in the cascade, the formation of fibrin from fibrinogen:*

[Diagram deliberately omitted from abridged version].

6.15.1 the intrinsic pathway begins with contact activation of Factors XII and XI, prekallikrein, and high-molecular weight kininogen (HMWK) that interact to activate FX to FXa;

6.15.2 the extrinsic pathway begins with trauma to tissue causing exposure of tlssue factor (TF) and activation of Factor VII to FVl!a. The TF/FVlla complex plus calcium, in turn, also activates FX to FXa;

6.15.3 the common pathway is where the intrinsic and extrinsic pathways converge on activation of FX to FXa which is the 'anchor' for formation of the prothrombinase complex (composed of FXa, FVa, phospholipids, and calcium ions) that catalyzes the activation of prothrombin to thrombin which, in turn, catalyzes flbrinogen to fibrin:

[Diagram deliberately omitted from abridged version].

6.16 The cascade/waterfall model of coagulation. In this model, coagulation is initiated by either the intrinsic or the extrinsic pathway, both leading to the formation of fibrin via a common pathway involving FXa, phospholipids, and calcium. The dotted lines indicate FXa and thrombin's positive feedback effects of FV and FVIII activation. From: Leblond L, Winocour PD. Chapter 1: The coagulation pathway and antithrombotic strategies, Antithrombotics, 1999.

6.17 Fibrinolysis is a process that prevents blood clots from growing and becoming pathogenic and removes clots once the underlying damage has been repaired. The cells of injured blood vessels release plasminogen activators (tissue plasminogen activator (tPA), urokinase) and the blood contains plasminogen. All of these proteins are serine proteases. Plasminogen and tPA bind to fibrin where tPA converts plasminogen to the active enzyme plasmin. Plasmin in turn lyses fibrin forming fibrin degradation products.

AVAILABLE ANTITHROMBOTIC/ANTICOAGULANT AGENTS AT RELEVANT DATE

6.18 Warfarin

6.18.1 One of the first anticoagulants developed as a therapeutic agent was warfarin. At the Relevant Date it was the only effective oral anticoagulant available.

6.18.2 Warfarin was discovered following the observation that cattle were dying from uncontrolled blood loss after eating mouldy hay from clover crops. Scientists from the University of Wisconsin studied the spoiled clover hay and eventually managed to extract a compound which was later named dicoumarol. After many more years of research, and further refining of the compound, a chemist from the University of Wisconsin, managed to synthesise a more potent anticoagulant from dicoumarol which was named warfarin. Warfarin was first registered in 1948 for use as a rat poison. In 1954 warfarin was first approved for medicinal and therapeutic use.

6.18.3 Warfarin and related coumarins (dicoumarol-type) are vitamin K antagonists. They act indirectly on the coagulation cascade because several coagulation factors require normal function of vitamin K for their synthesis. Thus, warfarin reduces the liver's ability to synthesize clotting factors, such as prothrombin, FVII, FIX, and FX. This results in lower concentrations of clotting factors in the blood and, thereby, makes it more difficult to form blood clots. Warfarin, however, also reduces naturally occurring anticoagulants (such as proteins C and S) that are Vitamin K dependent which could make it easier to form blood clots. Consequently, combined

with some of the other issues for warfarin summarized below, predicting its net effects was not always straightforward.

6.18.4 *The major advantages of warfarin are its potency as an anticoagulant, oral effectiveness and long duration of action (it only has to be administered once a day). However there are a number of disadvantages to warfarin treatment:*

(a) The mechanism of action means that the anticoagulant effect does not occur immediately after administration of warfarin. It takes 24-72 hours for onset of action and therapeutic effect is not seen until 5-7 days after initiation of treatment. This means it is not suitable to treat acute thrombotic events.

(b) Bleeding is the major clinical problem associated with the use of warfarin. This can be a problem for patients who may suffer major bleeding from small injuries or internal bleeding. The major concern is an intracranial hemorrhage (a stroke caused by bleeding in the brain). This occurs in <1% of patients but can be fatal.

(c) The anticoagulant effect of warfarin is not readily reversible. This can be a problem, for example, if a patient on warfarin needs emergency surgery when it is not possible to wait until the warfarin is fully out of theit system and they may bleed excessively during surgery.

(d) Because its effect is mediated via vitamin K which is present in the diet to varying amounts, there is marked variability in response both between different patients and even for the same patient over time, depending on their diet, co-existing medical conditions, other medications etc. This means it is not possible to adopt a one-dose-fits-all approach and the dose will have to be tailored to each patient, both initially and over time.

(e) Because of the high level of variability and the seriousness of bleeding as a side effect, treatment with warfarin requires all patients to undergo routine monitoring of their blood to assess the prothrombin time (PT). This is a measure of how long it takes the blood to clot; if it takes too long the patient is at risk of excess bleeding. Patients do not like undergoing monitoring and it is a burden for health care systems.

6.19 *Heparin*

6.19.1 *Heparin was the anticoagulant agent of choice when a rapid antithrombotic response was required. Heparin is a mixture of highly sulfated polysaccharide chains ranging in molecular weight from 3000 to 30000 Da, with a mean of 15000 Da. Heparin inactivates thrombin, as well as the coagulation factors IXa, Xa, Xia, and Xlla, by accelerating their reaction with the physiological inhibitor Antithrombin Ill (ATIII).*

6.19.2 *Heparin has a number of disadvantages:*

(a) It needs to be administered parenterally (by injection). This means it is not suitable for long term at home use by patients.

(b) Heparin binds avidly to plasma proteins, thereby requiring frequent monitoring due to its unpredictable pharmacokinetics.

(c) It is ineffective in patients with ATIII def1eiencies so other rapid onset anticoagulants are required for these patients.

(d) ln a small but significant number of patients (reported incidence varies from 0.1%- 5% of patients) heparin can cause heparin induced thrombocytopenia (reduction in platelets), which is a potentially fatal

complication of heparin therapy.

(e) Heparin's anticoagulant function is neutralized by platelet factor 4 (PF4) released from activated platelets. In addition, thrombin bound to fibrin in thombi or to the exposed subendothelial matrix (in damaged blood vessel walls) remains active and is resistant to heparin-ATIII inhibition.

(f) Low molecular weight heparins (LMWHs) were also available at this time. LMWH preparations are fragments of standard heparin produced by controlled chemical or enzymatic depolymerization. They are heterogeneous in size, ranging in molecular weight from 1000 to 10000 with a mean of 4000-5000. They exert their antithrombotic effect primarily by accelerating antithrombin Ill-mediated inhibition of FXa and are frequently used to treat and prevent recurrence of deep venous thrombosis (DVT). The LMWHs overcome some but not all of the disadvantages listed above for heparin. They have good pharmacokinetic properties which result in predictable anticoagulant responses to weight-adjusted dosing. They are associated with lower bleeding risks than heparin due to a lack of effect on platelets or vascular permeability. Administration is generally by subcutaneous injection, however, which can be a challenge for some patients.

6.20 Rationale for FXa inhibitors

6.20.1 There are a number of places in the coagulation cascade that could be targeted by inhibitors with a view to inhibiting coagulation. Two that were of particular interest were thrombin and FXa.

6.20.2 The position of FX at the start of the common pathway makes it a particularly critical clotting factor just 'above' thrombin in the coagulation cascade (Figure 1). When activated, FXa catalyzes the formation of thrombin from prothrombin (the inactive form of thrombin). However, when complexed in the prothrombinase complex with FVa, phospholipids, and Ca^{2+}, FXa's ability to activate thrombin from prothrombin is amplified approximately 300,000-fold (see pages 410-414 Antithrombotics, 1999 for additional details). Accordingly, it was considered important for an effective FXa inhibitor to inhibit FXa in the prothrombinase complex even more than free FXa since this complex activates most of the prothrombin to thrombin in the coagulation cascade.

6.20.3 FXa was considered to be a better target than thrombin by some investigators, including the Parke-Davis group and its partners at Biochem Pharma and Schering AG. Inhibiting FXa was expected to be more effective than inhibiting thrombin because blocking one molecule of FXa effectively inhibits formation of thousands of thrombin molecules. Therefore, it was thought that lower doses of FXa inhibitors might be effective. In addition, there was hope that bleeding side effects would be less with FXa inhibitors. Some animal experiments supported this but it had not been definitively established by the Relevant Date.

6.20.4 The initial proof of principle regarding targeting FXa came from well-known naturally occurring FXa inhibitors such as tick anticoagulant peptide (TAP) and antistasin (ATS). Both are highly selective, very potent direct inhibitors of FXa. Recombinant (i.e. versions made in the lab) versions of these peptide inhibitors were also developed. However, recombinant proteins are not ideal drug candidates because they are relatively large making oral bioavailability unlikely and the body is full of enzymes which naturally break down proteins. Therefore, synthetic, small molecule, nonpeptide FXa inhibitors were the goal of many research teams.

6.20.5 FXa inhibition was the target of a lot of research and development efforts in the 1990s and into the 2000s. The search was on to identify potent, selective,

small molecule (ideally less than MW of 500 or so) inhibitors of FXa that were orally bioavailable to provide a replacement for the only orally active anticoagulant available at this time, warfarin. An expected advantage of small molecule inhibitors was that, unlike heparins which are very large molecules dependent on interaction with antithrombin Ill, small molecules are more likely to be able to get into an existing clot to prevent it growing. Once within the clot small molecules would also be better able to access the active site of FXa within the prothrombinase complex.

6.20.6 By the Relevant Date a number of candidate compounds had undergone fairly extensive preclinical evaluation in animal studies that were reported in the literature. One early lead candidate was the Daiichi compound, DX-9065a. It was a potent (Ki value 40 nM against FXa) and selective inhibitor of FXa and effective in a number of animal models of thrombosis and there were also claims that it was orally bioavailable. The inhibitory activity of DX-9065a was compared with that of the larger molecules of heparin plus antithrombin Ill (which is necessary for heparin's anticoagulant effects) on FXa in the fluid phase, FXa before or after assembly in the prothrombinase complex, and FXa in the prothrombinase complex during initiation of prothrombin activation to thrombin. DX-9065a and heparin- antithrombin III had comparable inhibitory effects on free FXa (in the fluid phase or before prothrombinase assembly) but DX-9065a exerted substantially better inhibition of FXa activity when FXa was complexed into prothrombinase.

6.20.7 Selectide reported the discovery and optimization of active site inhibitors of FXa using synthetic combinatorial chemistry in the mid-1990s. Candidates included SEL-2711 (with a Ki value of 3 nM} and SEL-2684 (Ki value of 0.3 nM) which were also selective over thrombin and other serine proteases. Yamanouchi (focused on dibasic type FXa inhibitors) and Corvas (focused on argininal type transition state FXa inhibitors) also reported identification of small molecule lnhibitors. The literature also contained work on benzamidine and bisamidine structures that might prove useful as FXa inhibitors. (See Chapter 14, Antithrombotics 1999 for more details).

6.21 Design and development of enzyme inhibitors

6.21.1 The FXa inhibitor field was fairly advanced by 2001 and so the necessary properties of a potentially useful FXa inhibitor ·would have been part of the CGK of the skilled pharmacologist. The role of the skilled pharmacologist was to determine the potency, selectivity, and biological activity of candidate FXa inhibitors.

6.22 Potency

6.22.1 Potency of an enzyme inhibitor refers to how strongly an inhibitor will block the normal function of an enzyme. The more potent the inhibitor the lower the amount that will be needed to achieve inhibition and therefore the lower the dose that should be required to achieve a therapeutic effect. While it is true that even a very weak inhibitor may in theory achieve an antithrombotic effect if given at sufficiently large amounts, this creates problems in terms of pharmacokinetics, physicochemical properties, safety and toxicity. Essentially, most drugs can be poisons if given at sufficiently high levels. There is also a maximum cut off in terms of amount of compound which can be administered to a patient. Most pills contain at a maximum 500 mg of

active ingredient. Above that level multiple, large pills need to be taken and that is not desirable for the patient or the manufacturer. Therefore, the key property of a potentially useful inhibitor is that it meets the relevant threshold for necessary potency.

6.22.2 *The widely accepted general principles related to potency were these:*

(a) The more potent the inhibitor, the smaller the dose required to achieve the desired antithrombotic effect.
(b) The antithrombotic effect of an inhibitor has to be balanced against its effects on hernostasis (normal clotting) so the lower the dose, the lower the likelihood of serious bleeding side effects.
(c) The lower the dose, the lower the likelihood of other side-effects that at this early stage in development would be hard to anticipate.

6.22.3 *Potency is measured by an enzyme inhibition assay. This allows determination of whether and how strongly a compound can inhibit the catalytic activity of an enzyme in vitro. As noted earlier (see Enzymes and Enzyme Inhibition section), a primary in vitro measure of potency is expressed as a K1value. The K1 is the concentration of inhibitor required to produce half maximal inhibition. The lower the K1 the less compound you need to inhibit the enzyme and, therefore, the lower the K1, the more potent the inhibitor. Standard screening assays would be routinely carried out using commercially available kits and apparatus. A related measure of inhibitory potency is an IC50 value (concentration at which 50% of the maximum effect is observed) which also provides a means to determine relative potencies. Since the patents under review only discuss K1determinations, I will concentrate on Kr as an index of potency.*

6.22.4 *Molar concentration (also called molarity, amount concentration or substance concentration) is a measure of the concentration of a chemical species, in particular a solute in a solution, in terms of the amount of the substance per unit volume of a solution. In chemistry, the most commonly used unit for molarity is the number of moles per liter (mol/L). If a solution with a concentration is said to be 1 molar, it is commonly designated as 1 M. In this report, you will see frequent references to concentrations expressed as µM (micromoles/L or 10^{-6} moles/L) and nM (nanomoles/L or 10^{-9} moles/L) to discuss the potency of inhibitors, expressed as a Kr value (the concentration of an inhibitor which produces half maximal inhibition). The lower the K1 value, the lower the concentration of the inhibitor required to inhibit an enzyme which means lower K1 values indicate higher potency of inhibition. So, for example, if the Ki of an inhibitor is 1 nM (concentration of 1 x 10^{-9} moles/L), that means it is 100Dx more potent than an inhibitor with a Ki of 1 µM (concentration of 1 x 10^{-6} moles/L).*

6.22.5 *The standard test to determine a Ki value for enzyme inhibition was to carry out a chromogenic assay. This is a simple assay in which the test compound is added to a solution containing the enzyme of interest along with a synthetic substrate in, for example, 96-well plates. The substrate is designed so that when it is acted on by the enzyme there is a color change which can be measured spectrophotometrically.*

6.22.6 *As a first pass screen or at the start of a research project, an initial Ki threshold value of 10 µM or less might be set to designate which compounds to discard and which to continue developing. Medicinal chemists would use the structures of compounds that met the threshold values as starting points to synthesize more compounds that, ideally, would show higher potency.*

6.22.7 For potentially useful small molecule FXa inhibitors, the consensus was that the level of potency we needed to achieve was in the low nM or even sub-nM Ki range. The reasons for this include the following:

6.22.8 First, as explained above, the prothrombinase complex can catalyze formation of about 300,000 more thrombin than free (or uncomplexed) FXa. Therefore, an effective FXa inhibitor has to inhibit the prothrombinase complex. The type of direct inhibitors which occupy the active site of prothrombinase are in competition with the natural substrate, prothrombin. In order to be effective, the competitive inhibitor must occupy the active site in preference to prothrombin.

6.22.9 There are two chief parameters which determine whether the inhibitor will bind to the enzyme in preference to the natural substrate. The first parameter is the relative concentration of the natural substrate versus the concentration of the inhibitor at the enzyme. The concentration in blood for prothrombin is about 1.5 μM based on Rosing J, Tans G, Govers-Riemsag JWP, Zwaal RFA, Hemker HC: The role of phospholipids and Factor Va in the prothrombinase complex. J Biol Chem 255: 274-283, 1980 ('Rosing, 1980') (Appendix 2). The second and more important parameter is affinity of the inhibitor vs the natural substrate for the enzyme. As explained above, inhibitor potency is usually conveyed with the parameter Ki which is the dissociation constant describing the binding affinity between an inhibitor and lts target enzyme. The parameter that is used to describe the kinetics of substrate/enzyme interaction is Km (the Michaelis constant) which gives the substrate concentration at which half of the maximum enzymatic reaction rate is attained. ln principle, the Ki of a direct inhibitor should be considerably lower than the Km of the natural substrate in order for the inhibitor to be effective. Since the Km of prothrombin for the prothrombinase complex is about 100-400 nM, Rosing, 1980 and Pusey ML, Nelsestuan GL: The physical significance of Km in the prothrombinase reaction. Biochem Biophys Rec Comm 114: 526-532, 1983 ('Pusey, 1983') (Appendix 3), the Ki of direct inhibitors needs to be considerably lower for there to be effective inhibition.

6.22.10 Second, the screening assays used to determine the Ki of inhibitors against purified enzymes in relatively simple solutions and using chromogenic substrates provided useful information. The conditions of the assays were a long way, however, from reflecting the actual physiologic circumstances in which the inhibitors would be expected to operate. Consequently, there was a tendency to overestimate potency in the screening assays because the test systems were set up to be relatively rapid and convenient rather than realistic. Ex vivo tests of coagulation parameters in plasma or in whole blood from intact animals represent much more complicated biological systems in which inhibition of FXa in the prothrombinase complex is a critical element. Potential binding of a FXa inhibitor to plasma proteins can confuse the issue further. These considerations added to the impetus to identify low nM inhibitors since we could not be certain how precisely the screening assays predicted behavior ex vivo {plasma or whole blood) or in vivo (in animal models).

6.22.11 Third, there is a practical consideration related to dosing in humans. In general, a less potent drug would have to be administered at a higher dose which could be onerous for patients and, importantly, a hlgher dose may increase the likelihood of side effects. An inhibitor should be specific for the target enzyme and highly selective for the target enzyme over other related enzymes (as discussed in more detail in the next section). The higher the dose of the inhibitor that is needed, the higher the

concentratlon is likely to be in a patient's blood which could be associated with significant off-target effects and toxicity.

6.22.12 *Therefore, it was part of the CGK of the skilled team that for a compound to be potentially useful as an anticoagulant, it should have an in vitro Ki in the low nM or even sub-nM range.*

6.23 Selectivity

6.23.1 *Compounds which are potentially useful as FXa inhibitors also need to be selective for FXa over other enzymes in the body. As noted previously, FXa is a member of a large family of enzymes called serine proteases. Serine proteases are not only present in multiple parts of the coagulation cascade but they are ubiquitous throughout the body and regulate diverse functions. So it is crucial to make sure the compounds are very specific for FXa and do not inhiblt other serine proteases to any significant degree. This is because:*

(a) A general benefit for any enzyme inhibitor of being selective is to reduce the risk of side-effects and toxicity caused by interactions between the inhibitor and off- target enzymes.

(b) To have anticoagulant activity, an FXa inhibitor must be selective over other enzymes in the coagulation cascade to avoid the risk of inhibiting naturally anticoagulant enzymes (such as Protein C and Protein S) because to do so would directly counteract the desired property which is to act as an anticoagulant. Likewise, off-target inhibition of enzymes that are part of the fibrinolytic system (such as plasmin, urokinase and plasmakallikrein) would likely create problems in that clots would persist.

(c) lf not selective for FXa over other serine proteases and other enzyme targets, the concentration of the inhibitor would potentially be diluted by binding to those other targets. This may result in insufficient amounts of the FXa inhibitor available to bind the target (i.e., FXa in the prothrombinase complex) and such a non-specific inhibitor would not be expected to have the necessary anti-thrombotic effect.

(d) A lack of selectivity for FXa could lead to unwanted effects on bleeding risk by, for example, inhibiting serine proteases which have natural anti-coagulant effects (such as Protein C and Protein S).

(e) FXa is closely related to the enzyme trypsin which is present in the digestive tract. If an FXa inhibitor binds to trypsin to any significant degree it is likely that an insufficient amount would be absorbed following oral administration because it would bind trypsin in the gut.

(f) Clotting factors, including FXa, are serine proteases. Other serine proteases include chymotrypsin, trypsin, and elastase which are important pancreatic digestive enzymes and acrosomal protease which is an important element in sperm penetration of ova. Since serine proteases have certain structural elements in common across the whole class of these proteins, identifying an inhibitor specific for one serine protease (such as FXa) but not for other serine proteases is an important challenge to overcome to minimize the likelihood of side effects.

(g) A lack of selectivity for FXa would also make it difficult to interpret exactly how the inhibitor was exerting its effects.

(h) Selectivity is measured by carrying out a series of separate enzyme inhibition assays to find out the extent to which a compound of interest inhibits similar related enzymes. A FXa inhibitor would typically be screened for selectivity against other serine proteases such as thrombin,

trypsin, plasmin, and tPA. In the FXa inhibitor field in 2001, a compound would be considered selective if it has at least three orders of magnitude or more lower potency against these enzymes than against FXa. Therefore, for example, if the K; for an inhibitor of FXa is 1 nM, a demonstration of selectivity requires that the K; of the inhibitor against other serine proteases such as thrombin or trypsin to be 1 μMor, ideally, even higher.

6.24 Biological activity

6.24.1 *The next task of the skilled pharmacologist would be to test candidate compounds in biological systems such as plasma, blood, and animals to see if the compound reduces clot formation. The K1 values derived from assays described above can ldentify promising inhibitors but to find out if they are effective antithrombotic agents requires getting closer to actual physiologic conditions by seeing if the compounds have an anticoagulant effect in plasma and blood.*

6.24.2 *These tests include the activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), and activated clotting time (ACT). In basic terms, blood or plasma would be obtained from a subject (animal or human) and the test compound would be added. Clotting would be induced and the time taken to form a clot measured. If the compound has an anticoagulant effect the time taken for a clot to form will be longer in samples with the compound compared to a control with no test compound.*

6.24.3 *The next stage in development would be to establish if a compound is a potentially useful antithrombotic and requires studies in anesthetized animals which represent intact biological systems. To minrmize the numbers of animals required for this stage, only the most promising candidates would be used, those that met pre-set criteria for the in vitro and ex vivo tests and assays discussed above. The animal studies represent a critical step before taking FXa inhibitors forward into clinical evaluation in human subjects. They can provide evidence of effectiveness in intact biological systems, as well as provide some information on safety in terms of bleeding risk.*

6.24.4 *There are a number of animal models of thrombosis that can provide information on the dose-response relationships of experimental antithrombotics such as FXa inhibitors. For a pharmacologist, the animal models represent an 'acid test' for the potential utility of a FXa inhibitor. Establishing clinical effectiveness, of course, requires a full development programbut the early evaluations, in animal models, determine whether or not there will be a program.*

6.24.5 *One frequently used animal model of coagulation was the rabbit arterio-venous shunt model which is described in both patents. Other types of animal models include stasis- induced thrombosis after injection of FXa in rats, thromboplastin infusion into rats, arterio- venous shunt in rat (carotid artery to jugular vein), hemodialysis in monkeys, veno-venous shunts in the abdominal vena cava in rabbits, and electrode induced thrombosis in the left circumflex coronary artery in dogs. The endpoints in these models varied but were generally some combination of time to clotting, clot weights, or changes in blood flow dynamics plus evaluations of standard clotting parameters and bleeding times. Different animal models were used because the effects of different agents on thrombosis in different settings (e.g., arterial vs venous) could vary. For example, a higher dose of an inhibitor might be required to inhibit thrombosis in an artery (with high flow, high shear, and large platelet component) compared to that required in a vein (high flow but low shear and low platelet component).*

WO652 & WO131

7.1 I have been asked to consider and give my view on W0652 and W0131. I have set out below my view as to what each document would teach the skilled pharmacologist. I have considered the disclosure of each of these documents independently only with the benefit of the CGK as it would have been at the Relevant Date.

7.2 Accordingly, I reviewed the patents as I believe a skilled pharmacologist would have done if they had been given each document (separately) and asked to evaluate what useful information each document contained for the skilled team looking to develop FXa inhibitors.

7.3 So, with the considerations summarized above in mind, the skilled pharmacologist would be asking the following questions of the patents: Does the patent provide information that the compounds of the invention are FXa inhibitors? To what extent does the patent provide information on the important properties the skilled pharmacologist would be looking for in a FXa inhibitor such as its potency against FXa, selectivity over other relevant serine proteases, and anticoagulant effectiveness in plasma, whole blood, or intact animals?

WO 03/026652 (BMS)

8.1 I conducted the evaluation of W0652 by reviewing the sections titled 'Field of the Invention', 'Background of the Invention', 'Summary of the Invention', and 'Definitions' but l concentrated on the 'Utility' section where most of the information relevant for a pharmacologist would be located. My observations are set out below.

8.2 Overall, W0652 would provide the skilled pharmacologist and medicinal chemists with a large group of chemical compounds on which to start the work to identify FXa inhibitor candidates. Other than that, however, W0652 does not provide information that would assist the skilled pharmacologist. Specifically, there were no data demonstrating useful levels of potency, selectivity for FXa above and beyond other enzymes, and no biological results on the bench or from animals.

8.3 Field of Invention

On page 1, W0652 states that "This invention relates generally to Jactam-containing compounds and derivatives thereof which are inhibitors of trypsin-like serine proteases, especially factor Xa... ". This is a reasonable assertion and could be correct. It stakes out the landscape of the invention and introduces the fact that the patent will be trying to corral certain types of chemical structures that could be tested for their potential utility to inhibit FXa. Determining if the goal of useful FXa inhibition is likely with the compounds under this invention would require substantial work to establish whether or not the properties of the compounds meet the expectations described above.

8.4 Background of the Invention

8.4.1 On page 6 is described the importance of identifying compounds that display 'improved FXa inhibitory activity and selectivity' versus other serine proteases. It also explains that it is desirable for FXa inhibitors to display other salutary pharmaceutical properties, dosage requirements, decrease clinical drug-drug interactions, and improve manufacturing

costs or feasibility.

8.4.2 These are all factors and concepts which were widely used in drug development (as well as the corporate requirement that production costs need to be kept reasonable). This conveys confidence that the patent writers had a good idea of the properties that would ultimately define a useful FXa inhibitor. These are items that would be on the agenda of any development team working on a project like this so they don't represent new information or guidance, .

8.5 Summary of the Invention

This section seemed to be what was required to make sure any invention would be associated with the appropriate steps to make it into an actual therapeutic agent. The patent states that the invention provides pharmaceutical compositions comprising a therapeutically effective amount of at least one of the compounds (or salt or prodrug thereof). In addition, the invention provides methods of treatment, administration, and therapy. This section concludes with the assertion that the novel lactam-containing compounds based on Formula 1 are effective FXa inhibitors. The summary of the invention is followed by a detailed description of preferred embodiments. These represent the aspirations of all drug development teams but there is not much information provided here or elsewhere in the patent to support high confidence those aspirations would be achieved.

8.6 Definitions

8.6.1 For the most part, this section seemed designed to make sure there was no ambiguity in the chemistry that would be presented in the patent.

8.6.2 On page 135 the patent states that 'Preferably the molecular weight of compounds of the present invention is less than about 500 grams per mole...' This represents an explicit statement that the goal was to find small molecules, consistent with earlier statements that they were targeting oral bioavailability. However, having a molecular weight of <500 does not guarantee or even provide any confidence that a molecule will be orally bioavailable. There are many other aspects to achieving oral bioavailability and in this field it proved to be a significant challenge.

8.7 Utility

8.7.1 As noted above, I expected the Utility section to contain most of the information that the skilled pharmacologist would be looking for, such as information that the invention actually included FXa inhibitors that were potent, selective, and worked in biological systems.

8.7.2 The Utility section begins with the claim that compounds of this invention 'are useful as anticoagulants for treatment or prevention of thromboembolic disorders in mammals', an effect believed to be due to inhibition of FXa or thrombin (page 168, lines 15-29, page 169, lines 1-21).

8.7.3 To the skilled pharmacologist, the word 'useful' in this sentence implies, first and foremost, that some compounds are demonstrated effective as antithrombotics in appropriate systems such as standard K; assays, clotting tests in plasma or blood, and, ideally, animal models. The skilled pharmacologist would therefore expect that the Utility section will provide support for this assertion that some compounds of this invention

are useful as anticoagulants.

8.7.4 An impressively complete list of potential clinical conditions for FXa inhibitors, including arterial and venous indications is included. At the Relevant Date all of these targets were potentially fair game for FXa inhibitors so they do not represent surprises. No guidance, however, is provided to help determine which of these potential clinical indications would be most likely to benefit from FXa inhibitors.

8.7.5 WO652 then describes a standard FXa assay using purified human FXa and the chromogenic substrate S2222 to estimate K1 values for compounds from the present invention (page 169, lines 22-36). The S2222 is a standard chromogenic assay which would have been familiar to the skilled pharmacologist at the Priority Date.

8.7.6 WO652 then reports at page 170 lines 21-32:-

(a) 'compounds tested in the above assay are considered to be active if they exhibit a K; of S.10 µM. Preferred compounds of the present invention have K;'s of s. 1 µM. More preferred compounds of the present invention have K,'s of s. 0.1 µM. Even more preferred compounds of the present invention have K;'s of s. 0.01 µM. Still more preferred compounds of the present invention have Ki's 0f'5:. 0.001 µM [sic];

and

(b) 'using the methodology described above, a number of compounds of the present invention were found to exhibit a K,s of s10 µM, thereby confirming the utility of compounds of the present invention as effective Xa inhibitors.'

8.7.7 WO652 reports that some compounds have a K1 value of 10 or less µM which, according to W0652, means that they were deemed to have utility as effective FXa inhibitors. It is correct that a standard first pass screening assay often uses a threshold Ki of 10 µM.

8.7.8 I have explained above as part of the CGK what the level of potency should be for the skilled pharmacologist to think that the compounds of the invention were credible potential drug candidates. A Ki of 10 µM does not meet this requirement. Instead, it represents a potential starting point for future work to modify structures and synthesize compounds with, ideally, more acceptable levels of potency.

8.7.9 Preferred thresholds (lower K1 values which corresponds to greater binding potency) are described in the patent which indicates the patent writers knew what the next steps had to be but not that any of their structures would necessarily meet the more stringent criteria. There were some pretty potent (K1 in the nM range) FXa inhibitors already being reported in the literature and being developed by companies such as Daiichi, Selectide, and Yamanouchi in the relevant timeframe, so WO652 would have made a more compelling case if more potent compounds from their invention had been mentioned. From the standpoint of a pharmacologist, if this patent was our starting point, it looked like, absent some good luck, we would have had a lot of catching up to do to be competitive.

8.7.10 WO652 then describes a rabbit arterio-venous shunt thrombosis model that could be used to evaluate the antithrombotic effects of compounds of the present invention. The principal endpoint is change in thrombus weight after 40 minutes of treatment which is used to estimate ID50 values for various compounds (page 170, lines 34-35, page 171, lines 1-

17).

8.7.11 The skilled pharmacologist would be familiar with this animal model and know it could be used for this purpose. However, the rabbit AV shunt model was apparently not used in WO652. This indicates to the skilled pharmacologist that the patent writers knew what an important next step should be but it would have been more reassuring to have seen some actual results. Even if the patent did include encouraging results from this particular model in rabbits, however, it would not have been all that striking since this model is a first stage animal model. Really exploring the potential of compound would require work in other animal models. Admittedly, no animal models predicted what would happen in humans with high precision, but some of them provided useful clues, for example, to help distinguish venous from arterial utility.

8.7.12 The chromogenic assay and the rabbit AV shunt are the only tests which WO652 describes in relation to FXa inhibitors. It does not describe any data generated from using either of these tests, nor any specific compounds to which such data would relate.

8.7.13 Regarding activity in biological systems, no standard coagulation parameters (such as aPTT, PT, ACT, TT) or even bleeding/clotting times were presented which would have been very instructive from the standpoint of a pharmacologist. A description of one animal model in rabbits that could be used to evaluate biological activity is included in the patent. This is one model among many that were available at this time. Since the model was described but not used, no results were presented that would have supported the claim that some of the compounds under the invention were effective antithrombotics.

8.7.14 WO652 then continues, claiming that some compounds may also be useful as inhibitors of serine proteases such as human thrombin, plasma kallikrein, plasmin, Factor VIia, Factor IXa, Factor Xia, and urokinase which may be useful for prevention or treatment of physiological reactions, blood coagulation and inflammation. 'Specifically, the compounds are claimed to have utility for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction and as reagents used as anticoagulants' in blood supplies (page 171, lines 18-30).

8.7.15 For a patent on FXa inhibitors, inclusion of this comment was a little surprising. Rather than explaining their position more clearly, this comment suggests that insufficient attention was being paid to the need for selectivity and seems to contradict remarks in the "Background of the Invention" that called for selectivity as a feature of their FXa inhibitor candidates. Recall that from the standpoint of a pharmacologist, the concept that inhibitors be specific for FXa and selective for it and not other serine protease inhibitors is of high importance. If the invention contains a lot of relatively unselective compounds, as these remarks could be interpreted to imply, the prospects for zeroing in on a useful and safe therapeutic agent might appear to a pharmacologist as somewhat remote.

8.7.16 Testing for selectivity is not a small undertaking. Selectivity requires determining Ki values for candidate compounds against a large number of enzymes, including the serine proteases mentioned in the patent but also many others that may cause side effects and safety problems if inadvertently inhibited. So the importance of appreciating the need for selectivity cannot be overstated.

8.7.17 WO652 then describes a standard thrombin assay using thrombin and the chromogenic substrate S2238 to determine in vitro Ki values. Some compounds of the invention exhibited Ki values <10 μM that, it was claimed, confirm the utility of the compounds of the present invention as effective

thrombin inhibitors (page 171, lines 31-36, page 172, lines 1-21).

8.7.18 The description of the thrombin assay appears to be correct. Why it is included in a patent focused on FXa inhibitors, however, is not clear. The fact that some compounds showed activity against thrombin is interesting but raises a question: were these the same compounds that showed activity against FXa? If so, this represents a demonstration of not particularly good selectivity for the target of FXa. If not, it still does not dispel concern that 'target promiscuity' could be an issue with this group of compounds.

8.7.19 WO652 then presents claims that the compounds of the present invention can be administered along with or in combination with one or more additional therapeutic agents, which will lead to prevention or amelioration of thromboembolic diseases or their progression. The lfst of additional agents include warfarin, heparin, other FXa inhibitors, antiplatelet agents (eg, aspirin, ibuprofen, ticlopidine, etc.), thrombin inhibitors, and fibrinolytics. A substantial list of other agents that can be used in combination with compounds of this invention is also provided, including anti-arrhythmics, anti- hypertensives, calcium-channel blockers, cardiac glycosides, duretics, mineralocorticoid receptor antagonists, phosphodiesterase inhibitors, cholesterol/lipid lowering agents, anti- diabetics, anti-depressants, and other agents to treat potential co-morbidities that might be encountered in patients with thromboembolic disorders (page 172, lines 22-36, pages 173-178, page 179, lines 1-16).

8.7.20 This struck me as probably necessary language in a patent to cast as wide a net as possible for how the compounds might be used. I can see the value of making these statements since the types of patients likely to benefit from FXa inhibitors would be likely to need some of these other kinds of drugs in co-administration settings. A big part of the development process, in fact, would be establishing what drugs could or could not be co-administered with FXa inhibitors that might emerge from this invention. The list provided is admirably complete but, until more information is available from studies of different sorts, is largely aspirational. From the somewhat narrower standpoint of a pharmacologist focused on the early elements of a drug development program (concentrating on potency, selectivity, and demonstrations of utility in biological systems, etc.), these claims were not particularly useful.

8.7.21 WO652 then describes three elements of other applications for the FXa inhibitors. These are:-

(a) (page 179, lines 17-25): Claim that the compounds of this invention can also be useful as standards or reference compounds in tests or assays involving inhibition of FXa.

(b) (page 179, lines 32-36, page 180, lines 1-5): Claim that compounds of the present invention may also be useful in diagnostic assays involving FXa.

(c) (page 180, lines 11-36, pages 181-187, page 188, lines 1-25): Descriptions of dosage and formulation options for compounds of this invention. The compounds can be administered orally (tablets, capsules, timed release formulations, liquid formulations), parenterally, and in combination products, etc.

8.7.22 These three elements of the Utility section are not particularly relevant from the standpoint of a skilled pharmacologist focused on the early stages of drug development.

8.7.23 In summary, for the skilled pharmacologist, WO652 would provide a large store of candidate structures to start the project to come up with a FXa inhibitor. The patent comes across as fairly generic in some places and quite

specific in others. A pool of chemical structures would be available to test under this patent and good descriptions of clinical settings where a FXa inhibitor might be useful are provided. As complete as the list of clinical settings (and also the list of drug interactions to avoid) was, this sort of information was already largely available. Medicinal chemistry would still have to go through the compound libraries to find promising candidates and Pharmacology would have a full agenda of in vitro, ex vivo, and in vivo tests to conduct.

WO 00/39131 (DU PONT)

9.1 I conducted the evaluation of WO131 by reviewing the sections titled 'Field of the Invention', 'Background of the Invention', 'Summary of the Invention', and 'Definitions' but I concentrated on the 'Utility' section where most of the information relevant to the skilled pharmacologist would be located.

9.2 Overall, the main thing this patent application would provide the skilled pharmacologist is a vast library of chemical compounds and the task of making and testing them. The information I was hoping to see (such as confirmation of useful levels of potency, demonstration that compounds were selective for FXa above and beyond other enzymes, or biological results on the bench or from animals) was not in the patent and it is not possible for a skilled pharmacologist to predict those properties just based on the names or structures of compounds.

9.3 Field of Invention

9.3.1 Their starting point appeared to be, sensibly, to start with serine protease inhibitors. It looks like they searched for any patents describing serine protease inhibitors of certain classes that did not include FXa (or thrombin) inhibition in the patent.

9.3.2 In so doing, the patent writers cast a wide net to corral as many structures as possible for potential use as FXa inhibitors against any and all thromboembolic disorders.

9.4 Background of the Invention

9.4.1 The Background section lists patents with the classes of chemical structures that qualified as nitrogen containing heterobicycles that did not stipulate use as FXa inhibitors.

9.4.2 A brief case for developing FXa inhibitors as anticoagulants (eg, the central role of FXa in the coagulation cascade, the possibility that FXa inhibition may be more efficient than thrombin inhibition) is also presented.

9.5 Summary of the Invention and Definitions

9.5.1 On page 3, the patent states that the inventors' discovery represent 'effective factor Xa inhibitors'. This seemed to be overstating their case somewhat. Later in the document it is mentioned that some compounds displayed Ki values against FXa that were 10 μM or less. This could provide a starting point for a project with the aim of developing potent selective compounds, but it does not really demonstrate effectiveness. That would require some relevant biological data for identifiable compounds. Instead the assertion that their invention is, in fact, 'effective' seems aspirational short of an actual demonstration of

effectiveness.

9.6 Utility

9.6.1 As noted above, I expected the Utility section to contain most of the information I was looking for as a skilled pharmacologist. I hoped to see information that made me reasonably confident the invention actually included FXa inhibitors that were potent, selective, and worked in biological systems.

9.6.2 It starts with a claim that compounds of this invention are useful as anticoagulants for treatment or prevention of thromboembolic disorders in mammals, an effect believed to be due to inhibition of FXa or thrombin (page 263 lines 1 -1 O). To the skilled pharmacologist, the word 'useful' in this context implies, first and foremost, that some compounds will be demonstrated effective: as antithrombotics in appropriate systems such as standard K1 assays, clotting tests in plasma or blood, and, ideally, animal models.

9.7 Potency

9.7.1 There follows a description of a standard FXa assay using purlfied human FXa and the chromogenic substrate S2222 to estimate K1 values for compounds from the present invention. As explained above this is a standard enzyme inhibition assay that the skilled pharmacologist would be familiar with. There is no value in describing the assay itself, what the skilled pharmacologist is interested in is results of the assay for compounds of the invention.

9.7.2 The passage goes on to state that (page 264, lines 1-10):-

(a) 'using the methodology described above, a number of compounds of the present invention were found to exhibit a Ki of 1:.10 µM, thereby confinning the utility of compounds of the present invention as effective Xa inhibitors'; and

(b) 'Compounds tested in the above assay are considered to be active if they exhibit a K1 of 10 µM. Preferred compounds of the present invention have Ki's of S1 µM. More preferred compounds of the present invention have Ki's of :::;o_1 µM [sic]. Even more preferred compounds of the present invention have K/s of :o;0.01 µM [sic]. Still more preferred compounds of the present invention have Ki's of so.001 µM. [sic]'

9.7.3 As explained above, a standard first-pass screening assay might use a threshold Ki of 10 µM but this falls a long way short of confirming the utility of a compound. To be useful, or put another way, to have utility a compound would need a K1 for FXa in the nanomolar range.

9.7.4 However, even if the Ki value claimed was sufficiently potent to be potentially useful, the patent doesn't provlde Ki values for any identifiable compounds, and it is not possible to speculate which compounds of the vast number disclosed have a Ki of 10 µM or less.

9.7.5 The statement that some compounds of the invention have a Ki of 10 µMor less suggests that there are compounds of the invention which have a Ki greater than 10 µM. These would not be considered FXa inhibitors even at the very low potency threshold of 10 µM.

9.7.6 Preferred thresholds (lower Ki values which correspond to higher potency) are described in the patent which indicates the patent writers knew what the

next steps had to be but not that any of their structures would meet the more stringent criteria.

9.7.7 At this time (2001) there were already some small molecule compounds with very low nM potency which were being reported in the literature and discussed at scientific meetings. Consequently, mentioning that some unidentified compounds in the invention met a first- pass screening threshold of 10 μM would not make any compounds of the invention potentially useful as antithrombotic agents.

9.8 Rabbit AV Shunt model

9.8.1 There follows a description of a rabbit arterio-venous shunt thrombosis model. The patent states that this model could be used to evaluate the antithrombotic effects of compounds of the present invention. The principal endpoint is change in thrombus weight after 40 minutes of treatment which is used to estimate IDso values for various compounds (page 264 lines 11-23).

9.8.2 The skilled pharmacologist would be well aware that this model could be used for this purpose but apparently it wasn't since no experimental results are reported. The absence of even a little information on biological activity for even a single identifiable compound of the invention in the patent was somewhat disappointing.

9.9 Inhibition of other enzymes

9.9.1 On page 264, lines 24-31 there is a statement that some compounds may also be useful as inhibitors of serine proteases such as human thrombin, urokinase, plasma kallikrein, and plasmin, which may be useful for prevention or treatment of physiological reactions, blood coagulation and inflammation. Specifically, the compounds are claimed

9.9.2 to have utility for the treatment of diseases arising from elevated thrombin such as myocardial infarction and as reagents used as anticoagulants in blood supplies.

9.9.3 For a patent on FXa inhibitors, inclusion of this comment was a little confusing. This comment suggests that insufficient attention was being paid to the need for selectivity. Recall that, from the standpoint of the skilled pharmacologist, the concept that inhibitors must be specific for FXa and not inhibit other serine protease inhibitors is of hfgh importance. Compounds which are not sufficiently selective for the target enzyme FXa over other, non-target enzymes could lead to serious side effects.

9.9.4 It is of particular concern to the skilled pharmacologist that it is stated that compounds of the invention might inhibit urokinase, plasma kallikrein, and plasmin. As explained above these are serine proteases whfch form part of the fibrinolytic pathway. If they were inhibited, normal clearance of clots might be impaired, thereby contributing to the persistence of pathologic thrombi.

9.10 Thrombin inhibition

9.10.1 It goes on to describe a standard thrombin assay using thrombin and the chromogenic substrate S2238 to determine in vitro K; values. It then states that some compounds of the invention exhibited Ki values <10 μM against thrombin and, it was claimed, confirm the utility of the compounds of the present inventron as effective thrombin inhibitors (page 264, lines 33-34, page 265, lines 1-16).

9.10.2 These remarks also came across as a little confusing since the avowed purpose of this patent is to find FXa inhibitors. It reduces confidence that the importance of specificity of FXa inhibition and selectivity versus other serine proteases (such as thrombin) was appreciated as well as it should be. Also, as explained above, the skilled pharmacologist was aware that direct inhibition of FXa was expected to have efficacy and safety benefits over direct thrombin inhibitors. The skilled pharmacologist would want to know which compounds inhibit FXa and which inhibit thrombin, but no data is provided for any specific compounds.

9.11 Administration in combination with other agents

9.11.1 Presentation of claims that the compounds of the present invention can be administered along or in combination with one or more additional therapeutic agents, which will lead to prevention or amelioration of thromboembolic diseases or their progression. The list of additional agents includes warfarin, heparin, other FXa inhibitors, antiplatelet agents (eg, aspirin, ibuprofen, ticlopidine, etc.), thrombin inhibitors, and fibrinolytics (page 265, lines 17-32, page 266, page 267, lines 1-15). -

9.11.2 This struck me as probably necessary language in a patent to cast as wide a net as possible for how the compounds might be used. I can see the value of making these statements since the types of patients likely to benefit from FXa inhibitors would be likely to need these other kinds of drugs, perhaps in co-administration settings. Part of the development process, in fact, would be establishing what drugs could or could not be co-administered with FXa inhibitors that might emerge from this invention.

9.12 Non-therapeutic uses

9.12.1 Claim that the compounds of this invention can also be useful as standards or reference compounds in tests or assays involving inhibition of FXa (page 267, lines 16-25).

9.12.2 Claim that compounds of the present invention may also be useful in diagnostic assays involving FXa (page 267, lines 26-32).

9.12.3 Descriptions of dosage and formulation options for compounds of this invention. The compounds can be administered orally (tablets, capsules, timed release formulations, liquid formulations), parenterally, and in combination products, etc (page 268-272).

9.12.4 As explained above, I consider that patent W0131 would be of interest to a team interested in discovery and development of FXa inhibitors for treatment of thromboembolic disorders (i.e., as potential drugs). Therefore, these three elements of the Utility section are not particularly relevant from the standpoint of the skilled pharmacologist focused on the early stages of drug development. However, even if these other uses were of interest to the skilled pharmacologist, there is no data in the patent to support any of these other uses.

WO 03 049 681 A2

11.1 *After formulating my views of WO131 and WO652 I was provided with and asked to then consider the following documents:*

11.1.1 *Patent application WO 03 049 681 A2 entitled 'Synthesis of 4,5-Dihydro-Pyrazolo [3,4-C] Pyrid-2-0nes' ('W0681') published on 19 June 2003*

with a priority date of 10 December 2001; and

11.1.2 *the Patent.*

11.2 *I was asked specifically to consider Example 53 of WO681 and the Claims of the Patent. I have been told and understand that the Patent is in fact the granted patent that arises from WO652.*

11.3 *Example 53 of WO681 describes the compound 1-(4-Methoxy-phenyl)-7-oxo-6-[4-(2-oxo-piperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylic acid amide (62) [Diagram deliberately omitted from abridged version].*

11.4 *Claim 1 of the Patent describes a compound which is represented by formula (1): [Diagram deliberately omitted from abridged version].*

11.5 *Having reviewed Example 53 of WO681 and Claim 1 of the Patent, I noticed that the structure as represented by formula (1) of Claim 1 of the Patent is the same structure as Compound 62 in Example 53 of WO681. A side-by-side comparison is set out in the table below. While the two structures are presented in a slightly different way the compounds are identical from a chemical point of view.*

[Diagram deliberately omitted from abridged version].

Statement #2 of 2

1. INTRODUCTION

1.1 *I am the same Kim P Gallagher who provided an expert witness statement on 14 April 2022 in these proceedings.*

1.2 *I have been provided with Professor Morrissey's report, along with the documents he provided and those with which he had been provided. I have also been provided with the expert reports of Dr Young and Dr Taft.*

1.3 *I have been asked to respond to Professor Morrissey's report. Additionally, while I understand that Teva has instructed witnesses to give evidence from the perspective of a skilled medicinal chemist and a skilled pharmacokineticist and that those experts will be responding principally to Dr Young and Dr Taft, I was asked to consider matters in their reports which may be relevant from a pharmacological perspective. In circumstances where I do not respond to any paragraph in the reports provided on behalf of BMS, I should not be understood to accept or agree with those paragraphs.*

1.4 *I understand my duty as an expert witness is to assist the Court on matters within my own expertise and that this duty overrides any obligation to the persons from whom I have received instructions and by whom I am paid.*

2. BACKGROUND AND QUALIFICATIONS

2.1 As summarized in the 'Professional experience and qualifications' section, Professor Morrissey and I were at the University of California, San Diego, at approximately the same time but I do not recall that we ever met while there.

3. SKILLED PERSON/SKILLED TEAM

2.2 In my report, I identified the skilled pharmacologist as a member of the skilled team. Professor Morrissey instead gives evidence from the perspective of the skilled biochemist. However, we both appear to agree on

the role which the skilled pharmacologist or biochemist would play within the skilled team and to a large extent agree upon the common general knowledge possessed by this skilled person. I shall continue to use the term "skilled pharmacologist" in this report but do not think that there is a significant disagreement between me and Professor Morrissey in this regard.

2.3 *Professor Morrissey states that the skilled team involved in the development of FXa inhibitors would include personnel with expertise in medicinal chemistry, biochemistry, and pharmacology (including pharmacokinetics). I explained in my report that the totality of a drug discovery and development team in the pharma industry would include, in addition to a medicinal chemist and pharmacologist, specialists of a broad membership, also including individuals from toxicology, pharmacokinetics, clinical studies, regulatory interactions, and marketing. However, as I also explained, neither WO131 nor WO652 contain information or data which is directed to these later elements of the development process. Therefore, I do not agree with Professor Morrissey's inclusion of a pharmacokineticist as part of the skilled team.*

4. PATENT AND APPLICATION

2.4 *The 'Patent and the Application' section of Professor Morrissey's report summarizes the main elements of the application that would be of interest to a skilled biochemist or pharmacologist. Since I indicated disappointment in my report that the Application provided little actual data, I found it noteworthy that Professor Morrissey also remarked that no data were provided for any compounds that were tested in vitro (see par. 85, p. 26) or in vivo (see par. 87, p.26).*

2.5 *In paragraph 88, Professor Morrissey states that it had been shown to him that 3.07g of the compound in Example 18 was synthesized. This was not something which I noticed when reading WO652, nor do I think this information would have been important to the skilled pharmacologist. The reason is that the synthesized quantity does not tell the skilled pharmacologist anything about the pharmacological properties of Example 18. The skilled pharmacologist is unable to make any sort of prediction as to the potency, selectivity or other characteristic of Example 18 without merely speculating.*

2.6 *Professor Morrissey continues in paragraph 88 to state that 3.07g would have been more than enough compound to run animal studies, including an AV shunt model. I agree that this quantity might have been sufficient for some testing. The amount of testing that would have been possible would depend on the biological properties of the compound including potency and selectivity. Therefore it is not possible to know what the extent of the testing might have been and the skilled person would need further information that is not in WO652 to determine the same.*

2.7 *Additionally, whereas WO652 indicates at p170, lines 28-32 that some compounds had been tested in the in vitro chromogenic assay for FXa inhibition, it merely provides a description of how the skilled team might perform tests with the rabbit AV shunt model without stating that any of the compounds had been evaluated using this in vivo test (see p170, line 33 - p171 line 1). Further, and as Professor Morrissey points out in paragraph 87, no data are provided from this animal model. Therefore, there is no indication that such a test was undertaken with Example 18 nor how it performed.*

2.8 *In paragraphs 89-91, Professor Morrissey discusses biological data about apixaban from a paper by Pinto et al. published in 2007, some six years after*

the Relevant Date at which I have been asked to consider WO652. As a preliminary point, the compound was not known by its generic name 'apixaban' in 2001. As Professor Morrisey notes, the compound is merely identified as 'Example 18' within WO652.

2.9 *At paragraph 90, Professor Morrissey presents the key findings from this 2007 paper by Pinto et al which demonstrate high potency, selectivity (relative to thrombin), good in vivo activity (rabbit AV shunt model), and a claim of oral bioavailability. As I explained in my first report, these are all attributes which the skilled team would be seeking in a drug development effort for a therapeutic FXa inhibitor.*

2.10 *Indeed, if data on high potency, selectivity, and in vivo activity had been included in WO652, I would have concluded WO652 made a strong case that its invention contained a promising FXa inhibitor.*

2.11 *None of this information, however, was presented in WO652. Based on what was stated in the document, there was no way to predict that Example 18 had these desirable pharmacological characteristics, including potency against FXa and selectivity (relative to thrombin or other enzymes). As I explained in my first report, in the pharma industry, most drug development projects fail. The probability of success, accordingly, starts low and moves up if and when positive experimental results (bearing on potency, selectivity, and in vivo activity) are generated and available for evaluation. The patent application did not include data like this.*

2.12 *At paragraph 90, Professor Morrissey states 'If the skilled team had carried out the standard...assays and the rabbit AV shunt model...in September 2001, they would have been expected to get the following results for apixaban'. I reiterate that these results were not published by 2001 and, based on what was stated in the Application, there was no way to predict Example 18 had these characteristics.*

2.13 *Further, in addition to stating that "a number of compounds of the present invention" were found to have a Ki of less than 10 μM against FXa, WO652 teaches at page 171, lines 31-32 that 'Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin ...'. It also explains, at page 169 lines 19-21, that 'The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.' As noted in my previous report, these kinds of statements confuse the issue and appear to contradict the objective, stated on page 6 of WO652, to identify compounds with '... selectivity for factor Xa versus other serine proteases ...' (page 6, lines 14-15). The statements suggests that insufficient attention was being paid to the need for selectivity for FXa.*

5. VALIDITY OF THE PATENT

2.14 *In paragraph 94 (page 28), Professor Morrissey states 'I have been asked to consider the question, whether, if a compound had been identified as being an effective factor Xa inhibitor in September 2001, the biochemist would anticipate that the compound would be a good candidate for a drug to treat thromboembolic disorders.'*

2.15 *I do not understand the assumption that Professor Morrissey has been asked to proceed upon. First, it is unclear what is meant in his report by an "effective" FXa inhibitor. As I explained in my first report, for a compound to be considered a potentially useful anticoagulant in therapy, it would need to have exhibited potency measured at a low or sub-nanomolar Ki, selectivity against other enzymes of at least three orders*

of magnitude (i.e., 1000-fold selectivity), and demonstrated biological activity in suitable assays. As set out in my first report, and as Professor Morrissey agrees, there are no such data in WO652 nor any such data which relate specifically to Example 18.

2.16 *Second, Professor Morrissey does not identify which person on the skilled team would assess whether an inhibitor is 'effective'. If 'effective' is understood in the way I have described above, it is the pharmacologist who would identify the characteristics of a FXa inhibitor which may be therapeutically useful, and perform and evaluate the in vitro and in vivo tests to establish whether a compound met those characteristics. This accords with the role and duties of the skilled pharmacologist (or biochemist) which I and Professor Morrissey appear to agree upon.*

6. DR YOUNG'S REPORT

2.17 *In paragraph 69, Dr Young considers the statement in WO652 that 'Compounds tested in the above assay are considered to be active if they exhibit a Ki of::; 10μM'. In relation to this statement, he comments that a '..compound with a Ki as high as 10 μMis unlikely to be a therapeutically effective factor Xa inhibitor..'. I agree with this statement and, in accordance with my first report, the skilled pharmacologist would require potency in the low nanomolar range to consider that a compound would have potential for therapeutic use.*

2.18 *At the end of paragraph 69, Dr Young refers to an 'effective' FXa inhibitor. He does not identify the properties which would be considered to make a compound 'effective' nor which member of the skilled team would identify the requirements for effectiveness. I repeat my comments made above in relation to Professor Morrissey's use of this phrase.*

2.19 *Dr Young also refers to the synthesized quantity of Example 18. As f have said above, I do not consider this information would be of interest to the skilled pharmacologist because it does not inform them about any of the pharmacological properties of Example 18*."

APPENDIX 5

Abridged Written Evidence of Mr Golian[19]

"*3.* *I have been asked to give an account of how decisions regarding how intellectual property is held are made within the BMS Group with particular reference to the intellectual property that was acquired as part of the acquisition of the DuPont pharmaceutical business in 2001.*

Du Pont Acquisition

4. *I am aware from my work for BMS Co that on 1 October 2001, the DuPont prescription drug business, including DuPont Pharmaceuticals Company, was acquired by BMS Co. Although I was not involved in this transaction at the time, when I joined BMS in July 2002, I was responsible for matters that had originated at DuPont Pharmaceuticals Company prior to the acquisition by BMS. I am also aware that on 1 October 2001, DuPont Pharmaceuticals Company changed its name to Bristol-Myers Squibb Pharma Company and that, as a result of the acquisition, Bristol-Myers Squibb Pharma Company became a wholly owned subsidiary of BMS Co - the ultimate parent company in the BMS Group of companies - as illustrated by the following diagram:*

[Diagram not included in judgment]

[19] Attachments to the original are not included in this abridged version.

Control of Bristol-Myers Squibb Pharma Company's IP assets

5. *From the commencement of my employment with BMS on 1 July 2002, my experience has been that decisions as to how intellectual property assets are to be held have been made by BMS Co for both it and its wholly-owned subsidiaries. Typically, these decisions are made by BMS Co's intellectual property lawyers, often in consultation with BMS Co's tax department and other areas of BMS Co's legal department. When I was working for BMS Co in Wilmington, for instance, Bristol-Myers Squibb Pharma Company did not have its own independent intellectual property lawyers or legal department. I have personally been involved in many such decisions regarding the holding of intellectual property that have been made by BMS Co over the years as part of my role as an intellectual property attorney at BMS Co since 1 July 2002.*

6. *As far as I am aware, prior to my arrival, it has always been the case that BMS Co has made the decisions as to how it and its wholly owned subsidiaries hold their intellectual property assets, including prior to its acquisition of the DuPont pharmaceuticals business.*

7. *This appears to me to be borne out by e-mails dated 19 October 2001 and 29 October 2001, which I have been shown and which are attached to this statement as appendix [PGl] and [PG2] respectively. I can see that both emails relate to the acquisition of the pharmaceuticals business of DuPont by BMS Co. The email dated 19 October 2001 was sent by a Robert Souka, who I am told was a member of the BMS Co tax department at that time, to Francis Rossi, who was a lawyer in the BMS Co legal department. The email includes summaries of the assets of several of the businesses that had then recently been acquired by BMS Co from DuPont, including Bristol-Myers Squibb Pharma Company which is summarised as follows:*

Bristol-Myers Squibb Pharma Company .

This is a Delaware partnership currently owned 50% by E.R. Squibb & Sons L.L. . and 50% by Bristol-Myers Squibb Pharma Holding Company LLC (BMS Pharma Holding entity 100% owned by ERS - but the ownership is subject to change). BMS Pharma Company' houses most of the intangibles, the acquired sites and realty (Billerica, Garden City, Experimental Station, etc.) and pharmaceutical operations formerly operated by DuPont. This company leases employees to BMS Pharma Research Labs and realty to BMS Medical imaging.

This is consistent with my understanding of what the situation was following the acquisition.

8. *The email dated 29 October 2001 is from a Mark Sobecki, who I am told was a lawyer with the BMS Co legal department at the time, and it forwards an email dated 24 October 2001 sent to him by Francis Rossi which in turn forwards a message from Margaret Yonco-Haines, who I recall as working in the BMS Co tax department around the time I joined BMS Co. The 24 October email forwarded by Mark Sobecki sets out a series of recommendations regarding 'legal ownership of patents and trademarks' in connection with the DuPont acquisition. In relation to the patents and trademarks of the pharmaceutical business, the recommended policy is stated as follows:*

(1) <u>Patents and trademarks related to the Pharmaceutical business</u> - Maintain legal ownership in Bristol-Myers <u>Squibb Pharma</u> Company (formerly <u>DPC)</u>. We believe that this is the entity where they currently reside, so this should involve only a name change. New patents and trademarks in the name of Bristol-Myers Squibb Company.

9. *The recipients of the email were invited to let Ms Yonco-Haines know if there are any issues or concerns.*

10. *I was not employed by BMS Co at this time, however I worked with or have encountered most of the recipients of this email and have had their roles at the time confirmed to me by my colleagues in BMS Co. In that regard, David Bonk was my one-over manager and head of the BMS Co patent department when I joined in July 2002. Mr Bonk has sadly passed away but was a lawyer in the BMS Co legal department in October 2001. Marla*

Mathias had left BMS Co prior to my commencement however I am told by my colleagues that she was Vice President and Chief Patent Counsel at BMS Co in October 2001. Based on my knowledge of David Bonk and what I have been told about Marla Mathias's role in BMS Co, their inclusion on this email, as part of a cohort of individuals involved in a decision in respect of ownership of the intellectual property of its newly acquired subsidiaries, is consistent with my experience in BMS Co, described above, where BMS Co intellectual property lawyers typically have central roles and responsibilities in such decisions. I worked for a number of years with Cory Zwerling who was President of Bristol-Myers Squibb Medical Imaging when I joined BMS Co, an entity that formed part of the DuPont acquisition, and who was in a role at BMS Co in October 2001 supporting the integration of the DuPont Pharmaceutical medical imaging business into BMS Co. I worked for a number of years with Nadine Flynn who was head of the BMS Co trademark department, and I am told that she was in this role in October 2001. I know Sandra Leung as being corporate secretary with the BMS Co legal department in October 2001. I know Raymond Keane as a lawyer with the BMS Co legal department, and I am told that he was in this role in October 2001. I am told that Alan Bauer was a BMS Co senior finance director in October 2001.

11. *The 24 October 2001 email reflects decision making by BMS Co as to the legal ownership of Bristol-Myers Squibb Pharma Company's intellectual property, and the putting in place a policy in that regard, consistent with my experience of BMS Co being the decision maker and having control over how the intellectual property assets of its wholly owned subsidiaries are to be held.*

12. *The same policy described in that email, whereby legal ownership of Bristol-Myers Squibb Pharma Company's pharma IP assets remained with that entity, and only required a name change from DuPont Pharmaceuticals Company to Bristol-Myers Squibb Pharma Company, was in place when I joined BMS Co on 1 July 2002. I was aware of that policy and recall being involved in the preparation and filing of paperwork to effect such name changes around the time I began in BMS Co. Effecting name changes was less costly and time consuming than it would have been to have Bristol-Myers Squibb Pharma Company assign all those rights to BMS Co, so there were practical benefits to that approach in circumstances where - in my experience and as appears from the October 2001 emails - BMS Co in any event had control over the ownership of those intellectual property assets such that it could have decided to have Bristol-Myers Squibb Pharma Company assign those intellectual property assets to it at a later date as and when required.*

13. *On 17 September 2002, international application PCT/US02/29491 was filed in the name of its inventors (for the US part) and BMS Co (for ex-US parts), claiming priority from US '165 and seeking registration as a European Patent among others (and which resulted in EP 1427415 and ultimately the Patent in suit). A copy of that international application which published as WO2003/026652 is included at appendix [PG3]. At that time, Bristol-Myers Squibb Pharma Company was a wholly owned subsidiary of BMS Co and was subject to its control and direction as I describe above.*"

APPENDIX 6

Abridged Written Evidence of Mr Granwell

"***5.*** **OPINION ON THE LEUNG REPORT**

5.1 *In commenting on the Leung Report, I will make an initial observation as to how MNCs dealt with valuable patents during the 2001/2002 period for U.S. federal income tax purposes under the U.S. Internal Revenue Code of 1986, as amended (the 'Code'), and the Treasury Regulations promulgated thereunder.[1] Intangibles, such as patents, are viewed as the main driver of value creation and competitive advantage to the legal owner, such as a pharmaceutical company, because of the monopolistic right to exclude others from making, using or selling an invention during the term of the patent. Thus, it has been my experience, that U.S. multinational corporations would take great care in considering how to deal with valuable patents within their corporate group; that is, they would carefully consider the documentation of intangibles and thereafter, how to structure the holding of intangibles within the corporate group for tax and commercial purposes so to align with their business model and to avoid needless risks.*

5.2 *Upon the acquisition of the DuPont Pharmaceuticals Company ('DPC'), the tax department of BMS Co. appears to have advised that DPC's IP should be maintained in BMS Pharma Company as that only would involve a name change of that company from DPC to BMS Pharma Company. The ostensible reason cited by Ms. Leung for that recommendation is set out in the concluding paragraph 20 of the Leung report and is as follows:*

> 'Again, BMS Co. was the ultimate parent company of BMS Pharma and was the beneficial owner of such IP assets and controlled how IP rights of its wholly-owned subsidiaries were held. There was no need for BMS Co. to place the IP assets acquired from DuPont in BMS Co. at any particular time because it maintained control over the IP at all times and could decide to have BMS Pharma assign those IP assets to it (or any other entity) whenever it wished to do so when it served a business purpose, as it did so here.'

I describe this assertion as the 'Asserted BMS IP Policy' in this report.

5.3 *I note that the only documents Ms Leung references as evidencing the Asserted BMS IP Policy are two emails from October 2001, despite describing it as a* 'longstanding general policy' *at paragraph 17. She notes that the emails relate to a series of recommendations from BMS tax colleagues in the BMS Co. tax department, which she avers are in accordance with the Asserted BMS IP Policy.*

5.4 *I also note from paragraph 25 of the Affidavit of Scott Brown sworn on 10 March 2023 that there is no written record of the Asserted BMS IP Policy as regards BMS Pharma Company. He avers,*

> *'25. To the best of my knowledge, information and belief, no written policy of the manner in which the intellectual property of Bristol-Myers Squibb Pharma Company was to be held has been identified… .'*

5.5 *During the course of my career in dealing MNCs and other taxpayers and tax planning for intangible assets, I have never come across the theory outlined in paragraph 20 of the Leung Report. The Asserted BMS IP Policy, as I describe it summarily, does not accord with how I understood MNC's (and others) dealt with patents for purposes of U.S. federal income taxation during the time period of the subject transaction, i.e., tax years 2001-2002.[2]*

5.6 *I explain the principle reasons below:-*

5.6.1 As an initial matter and, as outlined in paragraph 5.4 above, there was no written policy in BMS Co. that dealt with how DPC/BMS Pharma Company, the legal owner of the said 'IP assets' *and BMS Co., the ostensible beneficial owner of the IP assets, should deal with the*

IP or with one another.

5.6.2 *Under the Code and the Treasury Regulations thereunder, I am unaware of any statutory guidance (other than a trust arrangement, discussed below) as to how the legal owner of the IP and the beneficial owner of the IP would report their respective tax attributes, including income, deductions, credits, etc. from the ownership and/or exploitation of the IP.*

5.6.3 *The Code and the Treasury Regulations contain detailed rules about how a trust and its beneficiaries are taxed. In the instant case, based on the instructions that I have received, there is no evidence of a trust instrument in writing, such as a Declaration of Trust, executed by a settlor wherein the settlor transfers the legal ownership of the IP to a trustee who holds the trust corpus for the benefit of a beneficial owner, i.e., the beneficiary.*[3]

5.6.4 *Based on the foregoing, characterizing a parent corporation as a beneficial owner of the assets of a subsidiary corporation*[4] *within a multinational group would be unworkable in the context of accurately reporting income, deductions, and credits under the Code and the Treasury Regulations, as further explicated in the below paragraphs, absent a trust arrangement interposed in a multinational group, which, of itself, itself would be unprecedented.*

5.6.5 *Under the Code and the Treasury Regulations, among various types of transactions, the legal owner of the IP can:-*

(a) *Exploit the intangible itself, by, for example, using the IP in the manufacture and sale of products containing the IP;*
(b) *License the intangible to an unrelated or related party;*
(c) *Enter into a cost sharing arrangement*[5]
(d) *Transfer the legal ownership of the IP to a related party as a capital contribution;*
(e) *Sell the IP to an unrelated or a related party.*

5.6.6 *Each of the transactions described in the foregoing paragraph has tax planning opportunities and potential hazards. I am unaware of any regime (other than a trust arrangement) in the Code or the Treasury Regulations to properly report transactions if one had to determine tax reporting both for the legal owner and the beneficial owner.*

5.6.7 *In terms of structuring and/or exploiting IP, extreme care must be taken, particularly if IP legally owned by a U.S. entity were to be transferred or used by a foreign entity of the group.*[6] *The Code contains a number of anti-abuse provisions, which, depending on the form of the transaction, could implicate an 'exit' tax*[7] *or, more generally, could implicate the transfer pricing provisions (under Section 482) summarized below.*[8]

5.6.8 *Apart from the complex application of the transfer pricing provisions in general, summarized below, the Asserted BMS IP Policy of legal and beneficial ownership cannot be reconciled with the U.S. (and international transfer pricing rules) that apply to cross-border transactions, particularly high-value intangibles. In that regard:-*

(a) Section 482 authorizes the Internal Revenue Service to adjust the income, deductions, credits, or allowances of commonly controlled taxpayers to (1) prevent evasion of taxes or (2) clearly reflect their income;
(b) The Treasury Regulations under Section 482 generally provide that prices charged by one affiliate to another, in an intercompany transaction involving the transfer of goods, services, or intangibles, should yield results consistent with the results that would have been realized if uncontrolled taxpayers had engaged in the same transaction under the same circumstances (the 'arm's length' principle);
(c) In addition, Section 482 has focused particularly on transfer of intellectual property. It provides as follows:

> '[i]n the case of any transfer (or license) of intangible property ,,, the income with respect to such transfer or license shall be commensurate with the income attributable to the intangible.'

The purpose of this provision was intended to deal with transfers of U.S. developed

intangibles (including patents) to controlled affiliates offshore
(d) As applicable to tax years 2001-2002, the 1994 Treasury Regulations contain an ownership rule for intangible property:

> IDENTIFICATION OF OWNER – (a) LEGALLY PROTECTED INTANGIBLE PROPERTY. The legal owner of a right to exploit an intangible ordinarily will be considered the owner for purposes of this section [482]. Legal ownership may be acquired by operation of law or by contract under which the legal owner transfers all or part of its rights to another. Further, the district director may impute an agreement to convey legal ownership if the conduct of the controlled taxpayers indicates the existence in substance of such an agreement. See section 1.482- 1(d)(3)(ii)(B) (Identifying contractual terms).

Treas. Reg, § 1.482-4(f)(3)(ii)(A)

(d) *Section 482 and its underlying Treasury Regulations are complex. In certain cases, depending on the substance of a transactions, generally by reference to assets, activities, functions and risks, Section 482 can result in an allocation to the economic owner, rather than the legal owner, of income. See. Treas. Reg. § 1.482-4(f)(3)(i). The ownership and allocation rules are distinct.*
(e) *In my experience, I have never encountered a situation where for actual tax purposes a subsidiary corporation within a multinational group would be treatedas the legal owner of an IP right and the parent corporation would be treated as the beneficial owner.*

5.7 *Turning to matters corollary to the tax issues discussed, I make the following comments:-*
5.7.1 *I note from paragraph 51 of the Thomas Report that he is similarly of the opinion that the Asserted BMS IP Policy is not in accordance with U.S. federal law on patents as he concludes,* 'I therefore respectfully disagree that BMS Company could be regarded as the beneficial owner of the earlier filed patent application, as contended in the Holland Report (at paragraph 40). The US courts have persistently rejected the argument that a corporate parent possesses either legal or equitable ownership of a patent owned by its subsidiary. As a result, BMS Pharma Company, and not BMS Company, was the owner of the inventions claimed in the US165 filing as of 3 November 2001. Further, BMS Company did not, by virtue of a purported assignment in 2007, establish itself as a successor in title to BMS Pharma Company in a timely manner.'
5.7.2 *If Ms. Leung's control/beneficial ownership approach were to be followed, it could lead to numerous and perhaps unintended consequences, as reflected upon in the Thomas Report at paragraph 71. As outlined by Chief Justice Steele at paragraph 32 of the Steele Report* 'Further, the mere possibility for a corporate parent to instruct a subsidiary to assign an asset does not under the laws of Delaware, equate to an assignment actually carried out.' *That would likewise be insufficient from a tax law perspective when considering who owned the IP assets. Also, in that regard, I do not understand why the subsequent assignment in 2007 was required or repeated in 2016 as it appears inconsistent with the Asserted BMS IP Policy.*
5.7.3 *I agree with Professor Thomas (see paragraph 22 of his second witness statement of 16 June 2022) and Mr. Rasser (see paragraphs 5.3–5.6 of his witness statement of 15 April 2022) that there must be clarity, transparency and consistency of ownership of a patent not only from a commercial perspective, but also from a tax perspective so as to ascertain who is the 'true earner' of the income from the IP and to seek to avoid allocations under Section 482, particularly if the IP were to be used abroad by foreign affiliates. If any beneficial ownership concept were overlaid on the structure, there would be chaos from a federal income tax perspective, as the federal tax rules applicable to ownership and use of IP (then and now) already are complex and would become even more complex particularly if there were cross-border transactions.*

[Footnotes]

[1] The Code is contained in the U.S. Code: Title 26. Subtitle A – Income Taxes (§§ 1-1564). The United States Code is a consolidation and codification by subject matter of the general and permanent laws of the United States. A number of the Code sections are referred to in the discussion herein and are referenced by the Section number of the provision in the Code. Treasury Regulations are the tax regulations issued by the United States Internal Revenue Service, a bureau of the United States Department of the Treasury. These regulations are the Treasury Department's official interpretations of the Code and are one source of U.S. federal income tax law. Regulations are the highest administrative authority issued by the Treasury Department. They are published in the Federal Register and codified in Title 26 of the Code of Federal Regulations (C.F.R.). Treasury Regulation cited herein are cited as Treas. Reg. §.

[2] Please note that there have been numerous changes in the Code and Treasury Regulations dealing with various tax aspects relating to intangible property. I would note that none of these changes involved a structure wherein one company was a legal owner of a patent and another related company was a beneficial owner of the patent.

[3] The taxation of a trust and its beneficiaries is contained in 26 U.S. Code, Part 1 (Estate, Trusts, and Beneficiaries). §§ 641-685. Further, to my understanding, technically, a trust does not have to be in writing. However, execution of a trust would be difficult if not in writing, since in the declaration, the settlor would transfer legal ownership of the property to be placed in trust to the trustee and would name the beneficiary.

[4] This assumes that both the parent and the subsidiary are regarded entities for U.S. federal income tax purposes. From the information provided, there is no reason to think otherwise.

[5] Generally, as potentially relevant to an intangible, a cost sharing arrangement is an agreement for sharing the costs of development of one or more intangibles in proportion to the participants' shares of reasonably anticipated benefits from their exploitation of interests in any intangibles that are developed.

[6] There also are tax issues if IP were to be licensed, for example, by an unrelated foreign entity.

[7] Section 367(d).

[8] Note, most industrialized countries have similar transfer pricing rules, see OECD Transfer Pricing Guidelines for Multinational Enterprises and Tax Administrations"

APPENDIX 7

Abridged Written Evidence of Dr Kinkeldey

Report #1 of 2

"*Facts Surrounding the Chain of Priority of EP415*

19. From the documents I have reviewed, I understand that the two inventors, Pinto and Quan, filed US165 on 21 September 2001. According to the documents available they assigned their rights in US165, including their priority right, to Bristol-Myers Squibb Pharma Company ('BMS Pharma Company') within the priority year, on 3 November 2001.

20. The PCT Application which led to EP415 was filed in the name of BMS Company on 17 September 2002, claiming priority from US165.

21. Since the PCT Application was not filed by BMS Pharma Company (to which the priority right was assigned) but by BMS Company, the subject of my opinion will be whether, upon filing the PCT Application, BMS Company had the right to claim priority from US165.

The Law Related to the Right to Priority and Its Interpretation By the Case-Law of the BOA

22. The right to priority is governed by Article 87 EPC which goes back to Article 4 of the Paris Convention. In G2/98, the EBA of the EPO held:

> *'The EPC constitutes, according to its preamble, a special agreement within the meaning of Article 19 of the Paris Convention. Articles 87 to 89 EPC, which provide a complete, self-contained code of rules of law on the subfect of claiming priority for the purpose of filing a European patent application (cf. decision J 15180; OJ EPO 1981, 213)'. (emphasis added)*

23. In accordance with Article 87 (1) EPC:

> *'Any person who has duly filed, in or for (a) any State party to the Paris Convention for the Protection of Industrial Property or (b) any Member of the Worfd Trade Organization, an application for a patent, a utility model or a utility certificate, or his successor in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date offiling of the first application.' (emphasis added)*

24. Since then, various BoA have had to interpret Article 87 (1) EPC, in particular in order to decide on the question of succession in title (e.g. decisions T 205/14, T 1201/14). A quotation from page 403, 3rd paragraph of the Case Law Book of the Boards of Appeal, English version, Ninth Edition 2019 provides that:

> *'Considering the requirement that the right of priority must have been transferred before the filing date of the later European application, the board in T 1201114 took the view that, even if a retroactive transfer such as the* nunc pro tunc *assignment under US law invoked by the appellant was allowable under US law, it would not be acceptable under Art. 87(1) EPC 1973. The board also held that an implied transfer of a particular right could be accepted when it was sufficiently clear that the parties had formed*

an agreement and what they had agreed. The burden of proving a valid transfer of the right of priority lay with the proprietor since it was the one claiming that right. As to the standard of proof to be applied to an implied transfer by virtue of a general policy under German law, the board held that the circumstances of the case in hand required proof 'beyond reasonable doubt', as all the relevant evidence lay within the knowledge and power of only one party to the inter partes proceedings.' (emphasis added)

25 *From the above cited cases, lt becomes clear that Article 87 (1) EPC sets certain rules or requirements for claiming priority, including the question of succession in title. For example, from Article 87 (1) EPC it follows that there must have been a transfer of the right of priority before the filing date of the subsequent application. Furthermore, Article 87 (1) EPC requires that it has to be sufficiently clear that there was an agreement and what was agreed. The burden of proof lies on the proprietor if they seek to rely on the priority date rather than the filing date of the application.*

26 *For the sake of completeness, I would like to note that cases G 1/22 (referring decision T 1513/17 of 28 January 2022) and G 2/22 (referring decision T 2719/19 of 28 January 2022) are currently pending before the EBA. Although the referrals predominantly relate to the so-called 'joint applicants approach' which is not relevant for the present case, one of the questions referred to the EBA in these cases reads:*

> *'I. Does the EPC confer jurisdiction on the EPO to determine whether a party validly claims to be a successor in title as referred to in Article 87(1){b) EPC?'*

27 *In referring this question, the referring Board noted that T 844/18 of 16 January 2020 (CRISPR) had already decided on this issue:*

> *'24. Thus the Board concludes that the instances of the EPO are empowered and obliged to assess the validity of a priority right claim as required by Article 87(1) EPC.'*

28 *The referring Board decided to put this fundamental question of competence to the EBA nonetheless. lt is not certain that the EBA will even come to answer this question in view of the long-standing EPO practice and the clear decision in T844/18.*

29 *Formally, as long as the EBA has not handed down a different view in pending cases, G 1/22 and G 2/22, the ruling provided by T844/18 has to be observed which is that the EPO has jurisdiction to examine the validity of a priority right claim under Article 87 EPC.*

30 *For the purposes of the present case, I note that even if according to the EBA the EPO would not have jurisdiction to examine the right to claim priority (which seems an unlikely outcome to me), any court deciding on the validity of a European patent would still have to examine the right to claim priority/ succession in title under the applicable laws of the EPC (Article 87 (1)).*

Consideration of the Facts of the Present Case under EPC Law and Case-Law

31 *On the basis of the documents available it seems that the assignments of Pinto and Quan on 3 November 2001 to BMS Pharma Company meet the requirements of the EPC as interpreted by the case law of the BoA, i.e. it is clear that the right of priority was transferred before the filfng date (see above paragraph 24, emphasized wording).*

32 *However, in order for the priority claim of the PCT Application that resulted in EP415 to be valid, a further transfer from BMS Pharma Company to BMS Company would have been required within the priority year. The only information available about BMS Company and its involvement in any intellectual property rights are certain statements made by Mr Paul Golian in his witness statement dated 21 March 2022 delivered in the*

Irish Proceedings ('Witness Statement of Paul Golian'). While Mr Golian is currently the Vice President and Assistant General Counsel, Intellectual Property at BMS Company, at the time of the DuPont acquisition he was an intellectual property attorney at BMS Company.

33 *From a review of his witness statement, it is my view that there is no evidence that there was a transfer of the right to claim priority of US165 for the purposes of filing EP415 from BMS Pharma Company to BMS Company. As a consequence, since Article 87 (1) EPC, at a minimum, requires that there has been an assignment of the particular priority right in question and that this is proven it appears clear that none of these prerequisites seem to have been met in the present case.*

Equitable Title and the EPC

34 *Finally, in relation to equitable title, I am not aware of any EPO case law stating or confirming that having 'equitable title' is sufficient to qualify as a successor in title, let alone under the specific facts of the present case.*

35 *The only case that deals with equitable title that I am aware of is the very old case of J 19/87. As outlined below, the Board has made clear that the case is considered as very much turning on its facts.*

36 *ln that case, the Board held that:*

> *'according to the fully reasoned expert opinion (...), this assignment did have certain legal effects in spite of the fact that it had not been signed by Mr Belcher.'*

37 *It is clear that in J 19/87, there was an assignment that, although not signed by Mr Belcher in fact was executed by NRDC and therefore had certain legal effects as the Board put it. This assignment was entered on the UK Register of Patents…*

38 *After J 19/87, Boards have held with respect to that case:*

> *a This is a 'particular situation' that should 'not be taken out of its context but should be confined to the facts of that case' (T 577/11 at 6.6.2)*
> *b. 'The board notes that this conclusion [in J 19/87] was drawn from a situation in which the relevant assignment agreement, by which ownership was to be transferred was concluded prior to the filing of the subsequent application and was defective solely for formal reasons.'. (T 577/11 t 6.6.2)*
> *c. 'The formal defects in the assignment could have been remedied by the contracting parties at any moment after its conclusion, and this remedy was legally possible under English Law' (T 577/11 at 6.6.2)*
> *d The 'equitable assignment' was registrable on the UK patent register and registration had indeed taken place (T 577/11 at 6 6 2)*

39 *In conclusion, in my opinion, J 19/87 does not take away the basic requirements for succession in title under Article 87 {1} EPC as set out above.*

Conclusion

40. *In conclusion, applying Article 87(1) EPC (as interpreted by the EPO BoA) to the facts of the present case. I have seen no evidence at all that there has been a transfer of the right to claim priority from US 165 from BMS Pharma Company to the later PCT Application, BMS Company, for the purposes of filing the European patent application that was granted as EP415. Under these circumstances, it is my opinion that BMS Company could not validly claim priority from US165.*"

APPLICABLE LAW – US FEDERAL OR STATE LAW

1. *There are two court systems in the United States: federal courts, which operate under the federal laws of the US, and state courts, which operate under the laws of each respective state. All cases arising under US patent laws must be heard in a federal court.*
2. *Where applicable, the federal court will apply both state law and federal patent Jaw where issues of state law are intertwined with federal patent law issues. For example, in* Tyco Healthcare Group LP *v.* Ethicon Endo-Surgery*, 587 F.3d 1375 (Fed. Cir. 2009), the Federal Circuit applied Delaware contract law to construe an assignment allegedly transferring ownership of the asserted patents to the plaintiff, Tyco Healthcare. The Federal Circuit ultimately concluded that Tyco Healthcare had not shown that it owned the patents that it had asserted and therefore dismissed the case for lack of standing.*
3. *In the US, state law governs the ownership of property (including intellectual property) and the interpretation of contracts. Therefore, the question of who has legal title to a patent is a matter of state law (*Enovsys LLC *v.* Nextel Commc'ns, Inc.*, 614 F.3d 1333, 1342 (Fed. Cir. 2010)).*
4. *Notwithstanding the general applicability of state law to questions regarding ownership of property and the interpretation of contracts, federal law governs the way in which an assignment of patent rights (including the right to clalm priority) can be made.*
5. *The leading case in this area,* Board of Trustees of the Leland Stanford Junior University *v* Roche Molecular Systems, Inc, *583 F.3d 832,841 (Fed. Cir. 2009), aff'd, 563 U.S. 776, 131 S. Ct. 2188, 180 L. Ed. 2d 1 (2011), summarized the situation as follows:*

> *'[T]he question of who owns the patent rights and on what terms typically is a question exclusively for state courts ... However, this rule has exceptions; the question of whether contractual language effects a present assignment of patent rights, or an agreement to assign rights in the future, is resolved by Federal Circuit law.'*

6. *There is therefore an overlap between state law and federal law regarding the transfer of patent rights and the two must be considered together in order to determine whether a particular purported transfer of patent rights is valid.*

FEDERAL LAW - ASSIGNMENT OF PATENT RIGHTS

7. *Any transfer of the rights in present or future inventions or in or under present or future patents or patent applications under US law is governed by the combined effect of:*

7.1. *The state law of the agreement by which the rights in the same are said to be transferred; and*

7.2. *Federal law.*

8. *The applicable state law, here Delaware law, would govern the interpretation of particular contractual elements of an assignment. My analysis below focuses on the federal laws that govern an assignment of patent rights.*

An instrument in writing

9. *Federal law, arising from the United States Code, governs the transfer of patent rights. lt stipulates that these rights must be assigned by an '*instrument in writing*' (35 USC§ 261). The relevant provision is:*

> *'Applications for patent, patents, or any interest therein, shall be assignable in*

law by an instrument in writing'.

10. *The statute does not stipulate the form or the contents of the written instrument, and courts have held that this statute 'imposes minimal requirements for such [anJ assignment.' Software Rights Archive LLC v Google Inc., No. CIV.A. 2:07-CV-511, 2009 WL 901361, at *4 (E.D. Tex. Mar. 31, 2009).*

11. *The District Court in Schwendimann v. Arkwright Advanced Coating, Inc., No. CIV. 11-820 ADM/JSM, 2012 WL 928214, at *6 (D. Minn. Mar. 19, 2012) explained that the 'relevant inquiry is solely whether the purported assignment is in writing' and it went on to look at the meaning of 'an instrument in writing':*

> *'Without any express statutory definition, what is meant by an "instrument in writing" must be determined by reference to its ordinary meaning. Asgrow Seed Co. v Winterboer, 513 U.S. 179, 197 (1995) ('When terms used in a statute are undefined, we give them their ordinary meaning' J. The ordinary meaning of 'owning is an intentional reduction to tangible form.' (emphasis added)*

12. *Based on the information in the Documents, there is no purported tangible form of an assignment. The only information relied on is a supposed internal policy of patent ownership in an internal BMS Company email chain in October 2001. These showed that BMS Company had a right to call for such a transfer. There is no evidence or statement to support the proposition that this right was ever exercised prior to the filing date.*

COMMENTS ON THE EXPERT REPORT OF THE LATE JUSTICE HOLLAND

13. *I have had the opportunity to review the Holland Report which I understand was relied upon by BMS Ireland in the Italian proceedings. While I have the greatest respect for the late Justice Holland, I strenuously disagree with his conclusion that '*BMS could be characterized as the beneficial owner of the earlier filed patent application.*' (Holland Report, paragraph 40). On the contrary, the prevailing view of the US federal courts is that a parent corporation possesses neither legal nor equitable title in patents that are owned by its subsidiary. To the extent that Teva seeks to advance that position in the Irish Proceedings, I make the following points:*

14. *The great weight of legal authority has concluded that '*the mere fact that a corporation's subsidiary owns a patent is insufficient to establish that the corporation has equitable title to the patent.*' (*Digitech Image Techs., LLC *v.* Newegg Inc.*, 2013 WL 1871513 (C.D. Cal. 2013)). One Federal Circuit decision,* Spine Solutions, Inc. *v.* Medtronic SofamorDanek USA, Inc.*, 620 F.3d 1305 (Fed. Cir. 2010), addressed the possible ownership interests of both a parent and parallel corporation of the patent owner. In that case, Spine Solutions, Inc. (SSI) was the assignee of the '071 patent. SSI was also the child corporation of another company, Synthes, Inc. In addition, SSI had a parallel corporation, Synthes Spine, that was also owned by Synthes, Inc. After bringing a cause of action for patent infringement, SSJ sought to add Synthes, Inc. and Synthes Spine to the litigation as co-plaintiffs.*

15. *The Federal Circuit made short work of concluding that neither Synthes, Inc. nor Synthes Spine were owners of the '071 patent. With respect to the parent corporation Synthes, Inc.:*

> *'It is undisputed that SSI is the sole owner of the '071 patent. With respect to Synthes, Inc., SS/'s parent corporation, the record contains no evidence that Synthes, Inc. is an exclusive licensee of the '071 patent. In fact, the amended complaint does not even allege that Synthes, Inc. licenses the '071 patent. Given that nothing in the record indicates that Synthes, Inc. is an owner or exclusive licensee of the '071 patent, we agree with Medtronic that SSI failed to show that Synthes, Inc. had standing to bring this suit.' Id. at 1317-18.*

16. *With respect to the parallel corporation Synthes Spine, the Federal Circuit weighed the evidence before it as follows, id. at 1318 (citations omitted):*

> *'SSI acknowledges that there is no agreement, either oral or written, between SSI and Synthes Spine with respect to the '071 patent. However, SSI asserts that an 'understanding' exists within the Synthes family that Synthes Spine has the exclusive right to practice the '071 patent. SS/ points to deposition testimony from its corporate representative-Robert Donohue, the Chairman of SSI and Chief Financial Officer of Synthes, lnc.-that this 'understanding' is 'based on the fact that [Synthes Spine] has the exclusive right to market and distribute all spine-related products in the U.S.... I'm not aware of an expressed agreement that is oral or written. I believe it's an agreement between the parties based on the way Synthes is organized."*

17. *The Federal Circuit rejected the argument that an 'understanding' among distinct corporate entities somehow amounted to .a written assignment of rights, as the US patent statute requires. In reaching this conclusion, the Federal Circuit recognized that if it were to allow Synthes, Inc. and Synthes Spine to join the litigation, 'any company related to a patent owner' would be deemed to have an ownership interest in the patent, 'regardless of any actual agreement as to exclusivity.' The Federal Circuit particularly pointed out that mere evidence of the "organization" of three related entities did not somehow impart an ownership interest in one patent to each of them.*

18. *Another leading Federal Circuit case,* Abraxis Bioscience, Inc. *v.* Navinta LLC*, 625 F.3d 1359 (Fed. Cir. 2010), considered a complex series of transact1ons among related corporate entities. In that case, AstraZeneca ('AZ-UK') and Abraxis entered into an Asset Purchase Agreement on 26 April 2006. The agreement provided that AZ-UK 'shall cause' the transfer of three patents to Abraxis. However, at that time, those patents were owned by Astra Lakemedel Aktiebolag ('Astra L') and AstraZeneca AB ('AZ- AB'), not AZ-UK. AZ-UK subsequently attempted to assign the patents to Abraxis on 28 June 2006, even though it still did not own the patents. On 15 March 2007, Abraxis sued Navinta LLC for patent infringement on the three patents. On the same day, AZ-AB and Astra L assigned the patents to AZ- UK, but not to Abraxis. Subsequently, on 12 November 2007, AZ-UK finally assigned the three patents to Abraxis.*

19. *On its way to concluding that Abraxis did not qualify as an owner of the three patents on the date that suit was filed, the Federal Circuit explained, Id. at 1366:*

> *'Whether Astra L, AZ-AB, and AZ-UK are part of the same corporate structure and are not 'complete strangers,' therefore, is irrelevant because there was no valid written assignment to Abraxis. (See 35 U.S.C. § 261) (assignments of patents must be in writing) ...Common corporate structure does not overcome the requirement that even between a parent and a subsidiary, an appropriate written assignment is necessary to transfer legal title from one to the other.'*

Although the Abraxis *v.* Navinta *opinion spoke towards legal title, its reasoning and ruling-as well as the language in the earlier Spine Solutions opinion - makes plain that Abraxis did not possess equitable title either. Otherwise this litigation could have proceeded under this alternative ground, for the only remedy sought by Abraxis was equitable relief, namely, an injunction against future infringement. (See Id. at 1361-62 (noting that the accused infringer had not yet sold or offered to sell its generic product)).*

20. *Several district courts have built upon the analysis in* Spine Solutions *and* Abraxis *v.* Navinta *in other scenarios involving members of the same corporate family. In the* Digitech *v.* Newegg *case, Digitech was the owner of legal title to the '415 Patent, and was also the wholly owned subsidiary of Acacia Research Corporation. The two corporations shared the same physical address and place of business. The District Court*

*readily concluded that 'Acacia cannot be deemed to have equitable title to the patent merely because it owns and exercises control over its subsidiary.' Id. at *5. In reaching this conclusion, the District Court for the Central District of California recognized that the* 'Federal Circuit has never held that a corporate parent has equitable title in its subsidiary's patents.*' Id. Instead, the concept of equitable title has applied only to contractual arrangements to assign rights from an inventor to another entity.*

21. *Noting that US corporate law 'sets clear boundaries between parents and subsidiaries,' id., the court explained:*

> *'Patent rights are not acquired unless authorized by, and acquired in, the manner prescribed by statute. While Courts permit true equitable-title holders to proceed out of fairness, equitable rules were not intended to circumvent policies and rules having their source in the patent statutes. The Court cannot find that mere ownership of corporate stock can convey equitable title in a patent without contravening the clear restrictions of both corporations and patent law. Such a holding would lead to absurd results.'*

Id. at 5 (citations omitted). As a result, 'Acacia's parent-subsidiary relationship with Digitech did not convey any cognizable interest in the '415 Patent-legal or equitable.' Id.

22. *Other judicial decisions are to similar effect. For example, in* Top Victory Electronics *v.* Hitachi Ltd.*, 2010 WL 4722482 (N.D. Cal. 2010), the court rejected Hitachi's argument that it was the equitable title holder of the asserted patents that were owned by its subsidiaries HCE and HAD. Hitachi's argument was that the companies 'were closely intertwined by virtue of their parent/subsidiary relationship' failed to convince the court that Hitachi had any ownership interest in the patents whatsoever. Id. at 3-4.*

23. *Other cases reaching the same result include* Quantum Corp. *v.* Riverbed Tech., Inc.*, 2008 WL 314490 at *3 (N.D. Cal. 2008) (a company's control of its patent-holding subsidiaries does not convey standing);* DePuy, Inc. *v.* Zimmer Holdings, Inc.*, 384 F.Supp.2d 1237 (N.D. Ill. 2005) (corporate parent of wholly owned subsidiary lacks standing to sue when the subsidiary owns the patent);* Beam Laser Systems, Inc. *v.* Cox Communications, Inc.*, 117 F.Supp.2d 515, 520-21 (E.D. Va. 2000) {the sole shareholder of a patent-owning corporation does not possess equitable title of them); and* Steelcase Inc. *v.* Smart Technologies Inc.*, 336 F.Supp.2d 714, 719 (W.D. Mich. 2004) (with respect to Delaware corporations, '*a parent does not have equitable title solely by virtue of its ownership of the subsidiary.*').*

24. *I therefore respectfully disagree that BMS Company could be regarded as the beneficial owner of the earlier filed patent application, as contended in the Holland Report (at paragraph 40). The US courts have persistently rejected the argument that a corporate parent possesses either legal or equitable ownership of a patent owned by its subsidiary. As a result, BMS Pharma Company, and not BMS Company, was the owner of the inventions claimed in the US165 filing as of 3 November 2001. Further, BMS Company did not, by virtue of a purported assignment in 2007, establish itself as a successor in title to BMS Pharma Company in a timely manner.*

COMMENTS ON THE EXPERT REPORT OF DONALD S. CHISUM

25. *I have also had the opportunity to review the Chisum Report. I understand that Professor Chisum issued his statement in connection with proceedings in other European jurisdictions, and in response to the Thomas Italian Report.*

26. *I understand that the Chisum Report has not been delivered for the Irish Proceedings, but that it may be of assistance to the Irish Court for me to give my views of the issues raised and relied on by BMS Ireland and its expert witnesses in related proceedings in other jurisdictions and for this reason I address certain aspects of the Chisum Report here.*

27. *While I hold Professor Chisum in high regard as a senior member of our shared academic community, I respectfully disagree with his criticisms of the Thomas Italian Report.*

28. *The Role of Section 118 of the US Patent Act. Professor Chisum cites section 118 of the US Patent Act, as it was worded at times relevant here, as support for the 'principle that a person or entity may have equitable rights to an invention or patent right even there is no written assignment of legal title.' (Chisum Report, paragraph 10.) Section 118 was in fact a narrowly drawn provision that speaks to circumstances not relevant to the present matter. It provides in pertinent part:*

> *'Whenever an inventor refuses to execute an application for patent, or cannot be found or reached after diligent effort, a person to whom the inventor has assigned or agreed in writing to assign the invention or who otherwise shows sufficient proprietary interest in the matter justifying such action, may make application for patent on behalf of and as agent for the inventor on proof of the pertinent facts and a showing that such action is necessary to preserve the rights of the parties or to prevent irreparable damage; and the Director may grant a patent to such inventor upon such notice to him as the Director deems sufficient, and on compliance with such regulations as he prescribes.'*

29. *This statute thus made clear that if an inventor is either uncooperative or unavailable, the holder of equitable title in the relevant invention may prosecute a patent application in the US. My understanding is that neither of those circumstances apply here. And by its own terms, section 118 did not permit the prosecution of patent applications by purported equitable title holders in other circumstances-and in particular, where equitable title is claimed by a related corporate entity owns title to the invention.*

30. *As Professor Chisum noted in paragraph 10 of his opinion, the US Congress subsequently amended section 118 in order to allow anyone who 'otherwise shows sufficient proprietary interest in the matter' to also file for a patent. Perhaps this more comprehensive category could potentially include members of the same corporate family in appropriate circumstances, but that matter is not before this Court. In my professional opinion, however, US courts would not apply this more permissive filing standard to applications under the previous version of section 118.*

31. *The Role of Standing. In the Chisum Report, Professor Chisum summarily dismisses the long list of US judicial opinions holding that corporate parents do not hold equitable title in patents owned by their subsidiaries. In his opinion, because these rulings arose in cases that primarily pertained to standing, they are simply irrelevant to ownership. I respectfully disagree with this conclusion. Simply because a principle of law is frequently articulated within one context does not suggest that it does not apply equally in a related context.*

32. *This view also misapprehends the notion of standing. Whether an entity possesses standing to sue for patent infringement comprises a multi-component inquiry that ultimately requires a dispute that is 'definite and concrete, touching the relations of parties having adverse legal interests.'* MedImmune, Inc. *v.* Genentech, Inc.*, 549 U.S. 118, 127 (2007) (citation omitted). The dispute must also be '*real and substantial*' and '*admi*[t]* of legal relief through a decree of conclusive character, as distinguished from an opinion advising what the Jaw would be upon a hypothetical state of facts.' Id. An assessment of ownership forms one component of determining standing to sue for patent infringement, but it is one of several. Ownership is not the same as standing, and thus the standing cases discussing ownership cannot be dismissed because they supposedly deal with an unrelated issue.*

33. *Professor Chisum also asserts, in paragraph 16 of the Chisum Report, that section 261 of the US Patent Act is limited to determining whether a "patentee" has standing to sue for patent infringement. To the contrary, section 261 expressly refers to patent applicants. I further observe that a 'patentee' is simply a successful patent applicant, namely the inventor or the inventors, or alternately an assignee. The distinction drawn here is one without a dlfference. As Professor Chisum explains in his treatise, 8 CHISUM ON PATENTS§ 22.01 (2022):*

> *'The presumptive owner of the property right in a patentable invention is the single human inventor, in the case of a sole invention, or the several human inventors, in the case of a joint invention. The inventor or inventors may then transfer ownership interests by written assignment to anyone (including a corporation or other entity) and may in fact be under a legal duty to do so by virtue of a contractual or other obligation, as in the case of an employee who has signed a contract requiring that he/she assign inventions made during the course of employment.N [I assume the 'N' should be a single apostrophe].*

34. *I additionally note that US courts respect the formal differences between members of the same corporate family across the gamut of patent law issues. With respect to remedies, for example, sometimes one corporate entity owns patents while a related company manufactures and sells the patented products. If the patent owner prevails in an infringement suit against a competitor under these circumstances, US courts ordinarily refuse to award damages based on lost profits-after all, the patent owner itself made no profits from the patents to begin with. A reasonable royalty should be awarded instead. Arguments that lost profits should be available across various corporate organizational constructs are ordinarily to no avail. See* Mars, Inc. *v.* Coin Acceptors, Inc.*, 527 F.3d 1359, 1367 (Fed. Cir. 2008) (declining to award damages to a patent holding corporation due to the lost profits of its wholly owned subsidiary). See also* Poly-America, L.P. *v.* GSE Lining Technology, Inc.*, 383 F.3d 1303, 1311 (Fed. Cir. 2004) (separate members of a corporate family '*may not enjoy the advantages of their separate corporate structure and, at the same time, avoid the consequential limitations of that structure*...')*.

35. *Another topic where distinctions among related corporate entities matter include that of enforceability. In* Email Link Corp. *v.* Treasure Island, LLC*, 2012 WL 4482576 (D. Nev. 25 Sept. 2012), two patents with substantially similar claims were held by two companies with a common corporate owner. One of the patents, issued later than the other, was subject to a terminal disclaimer under the doctrine of double patenting. The District Court held that the later-issued patent was unenforceable because the two firms were distinct enterprises, despite having the same corporate parent. In reaching this result, the District Court cited* United States *v.* Bennet*, 621 F.3d 1131, 1136 (9th Cir. 2010), for the proposition that '[t]*oday, it almost goes without saying that a parent corporation does not own the assets of its wholly- owned subsidiary by virtue of that relationship alone.*' Id. at "4.*

36. *Yet another area showing the same respect for corporate boundaries is liability for patent infringement. As the Delaware federal district court confirmed recently, absent a special showing, parent corporations are not liable for infringements committed by their subsidiaries. See* M2M Solutions LLC *v.* Te/it Communications *PC, 2015 WL 4640400 at *3 (D. Del. 2015).*

37. *Although I will refrain from stepping through the entire range of patent law subjects for which corporate structure is relevant, I will provide my professional opinion that US courts respect the enterprise organization that patent holders-or their related entities-have themselves established. This uniform approach makes sense as a matter of innovation policy, for it makes little sense to have ownership of a particular invention, patent application, or patent depend upon which doctrine is being applied. To put the matter squarely, in the US at least, one person cannot be the owner of an invention, patent application, or patent with respect to one legal issue, while a different person owns it for another.*

38. *Other Cases Cited by Professor Chisum. In paragraph 4 of the Chisum Report, Professor Chisum cites* Schwendimann *v.* Arkwright Coating*, 959 F.3d 1065 (Fed. Cir. 2020).* Schwendimann *was a case involving standing to sue for infringement, and to the extent that Professor Chisum recognizes that this line of cases is highly pertinent to the present matter, I agree with him. I further observe that* Schwendimann *involved the interpretation of a written agreement transferring title to patent rights, and I also agree that a written instrument is required to assign patent rights under section 261 of the US Patent Act.*

39. *Professor Chisum cites* Dalzell *v.* Dueber Watch-Case Manufacturing Co.*, 149 U.S. 315*

(1893), in paragraph 6 of the Chisum Report. The Dalzell *decision involved a former employer's attempt to compel a former employee to assign patent rights based upon inventions ostensibly made during the course of employment, as well as alleged affirmative representatives that he would so assign the patent rights. In my professional opinion, this nineteenth century opinion, involving entirely dissimilar facts to the present matter, has nothing to teach us about the relevance of Delaware corporate law to the facts at hand.*

40. *Finally, in paragraph 22, Professor Chisum voices his opinion that* Abraxis Bioscience, Inc. *v.* Navinta *LLC, 625 F.3d 1359 (Fed. Cir. 201O} is not a leading case. Although whether a particular judicial opinion qualifies as a 'leading case' may be a subjective determination, according to the Westlaw database, the decision has been cited 975 times by different sources.*

41. *Evidence of an Assignment. Paragraph 17 of the Chisum Report asserts what appears to be an alternative argument to the one based upon a construct of Delaware corporations. There, he questions whether an email chain provided a written assignment sufficient to provide BMS Company with equitable title in the patents owned by BMS Pharma Company.*

42. *I agree with Professor Chisum that, as a general matter, an email chain could constitute an instrument in writing. However, I have reviewed the Golian Witness Statement. That Statement largely describes emails sent prior to Mr Golian's employment by BMS Company. None of these emails includes any language whatsoever that could be described as conveying intellectual property from one entity to another. Rather, Mr Golian and the other individuals described in the Golian Witness Statement appeared to operate under the assumption that title would be transferred merely by changing the name of the firm from DuPont Pharmaceuticals Company to BMS Pharma Company. I am unaware of any case or other competent legal authority in the US holding that a change in an enterprise's trade name somehow transfers title of property owned by that enterprise to another.*

ADDITIONAL REMARKS

43. *I wish to make two additional observations.*

44. *First, I am under the impression that the corporate organizational chart presented in the Holland Report provides a severely truncated account of the vast, global network of BMS corporations and other enterprises. As a result, BMS is essentially arguing that it possesses a patent interest in any one of the inventions owned by any of its subsidiaries anywhere in the world-likely comprising many dozens or hundreds of enterprises. Going forward, I see no further reason why the argument of BMS Ireland could not be extended to assert that any subsidiary owned by BMS Ireland possesses equitable title in inventions by any other member of its corporate family. This position would establish a very large number of potential owners of any BMS patent Either of these situations would conflict with the policy goals of making ownership of patent rights orderly and predictable.*

45. *Second, insofar as Teva seeks to rely on a view (as expressed by the late Justice Holland) that ownership issues pertaining to patents are merely technical, I respectfully disagree with that suggestion as a matter of Innovation policy. When a patent is infringed, the damage from that infringement may redound to many others besides the patent proprietor. Corporate entities that are related to the patentee, including suppliers, distributors and retailers, may suffer reduced sales or other financial harms. Yet none of those losses would be protected by the law if these related entities did not own the patent Knowing which enterprise actually possesses title to an invention prevents uncertainty and expansion of the patent right, and also allows the USPTO to set clear boundaries on who may acquire and assert a patent, and what potential harms that enterprise may suffer if the patent is infringed.*

CONCLUSION

46. *Section 261 requires a written agreement for applications for patent, patents, or any interest therein to be assigned from one entity to another. While the term "writing" is construed broadly, that writing must contain words of conveyance sufficient to transfer*

ownership. For the most part, state contract law governs the ownership issues resulting from assignments, in the sense that principles ofstate law are used to determine whether a contract has been formed, how the contractual language should be interpreted, whether the contract has been breached, and related issues. In the absence of a written assignment, US courts have refused to allow companies related to the patent owner to claim either a legal or equitable interest in that patent because the companies are commonly owned.

Statement #2 of 2

INTRODUCTION

1. *I am the same John R. Thomas who previously submitted an expert report on 14 April 2022 in these proceedings.*
2. *I have been provided with, and had the opportunity to review, the Statement of Professor Donald Chisum dated 13 May 2022 (the "Chisum Statement"). My review of the Chisum Statement confirms my earlier opinion that under US federal law, corporate parents do not possess equitable title to patents owned by their subsidiaries merely by reason of the corporate relationship.*

GENERAL OBSERVATIONS

3. *In general, although Professor Chisum asserts that judicial opinions pertaining to standing are irrelevant to the determination of equitable title in this matter, he continues to cite them in support of his contentions. See,* e.g., Schwendimann *v.* Arkwright Advanced Coating, Inc., *959 F.3d 1065 (Fed. Cir. 2020) (Chisum Statement at paragraph 16);* Arachnid, Inc. *v.* Merit Industries, Inc.*, 939 F.2d 1574 (Fed. Cir. 1991) (Chisum Statement at paragraph 21);* Steelcase Inc. *v.* Smart Technologies Inc.*, 336 F.Supp.2d 714 (W.D. Mich. 2004) (Chisum Statement at paragraph 46). In contrast, Professor Chisum does not cite a single source stating that equitable title determinations with respect to standing are limited to that context, or that the definition of equitable title differs elsewhere. As a result, I once again agree with Professor Chisum that the US judicial opinions discussing equitable title, whether in the context of standing or another issue, are highly probative and indeed dispositive of the issue of international priority presented in these proceedings.*
4. *Also, as a general matter, Professor Chisum provides succinct quotations from judicial opinions regarding the application of state law to ownership issues without explaining the context in which they arose. In doing so, Professor Chisum fails to acknowledge that the recognition of equitable title has been limited to circumstances where an assignment of patent rights affirmatively occurred. See, e.g.,* Digitech Image Techs., LLC *v.* Newegg Inc.*, 2013 WL 1871513, at *4 n.3 (C.D. Cal. 2013) ('The only Federal Circuit cases that recognize an equitable title to a patent involve contractual arrangements to assign rights in inventions between the asserted equitable-title holder and the inventor. The Federal Circuit has also alluded to equitable title where the rights to a patent are being held in a trust.');* Beam Laser Sys., Inc. *v.* Cox Communications, Inc.*, 117 F.Supp.2d 515, 520 n.6 (E.D. Va. 2000) ('*The only cases from the Federal Circuit recognizing an equitable title to a patent, of which the court is aware, involve a contractual arrangement between the party claiming to hold equitable title and the inventor, pursuant to which the inventor assigned his rights in any invention prior to the existence of an invention, and the assignee later—i.e., after the invention came into being—claimed to have equitable title to the invention.'*). I observe that Professor Chisum cites* Beam Laser *and the quotation above, in Sections 21.02 and 21.03 of Chisum on Patents.*
5. *The decision of Chief Judge F. Dennis Saylor IV of the US District Court of Massachusetts in* Maquet Cardiovascular LLC *v.* Abiomed R&D, Inc.*, 2018 WL 4211364 at *4 (D. Mass. 2018) is instructive on this point. He there explained that the '*Federal Circuit has recognized that a party may hold equitable title to a patent without holding legal title to it, either because the party with legal title only acquired it by breaching a contract with the equitable title

holder or because the party with legal title improperly failed to name the equitable title holders as inventors.*' Maquet Cardiovascular LLC v. Abiomed R&D, Inc., 2018 WL 4211364 at *4 (D. Mass. 2018). Chief Judge Saylor further reasoned, id.:*

> *'*The Court is wary of extending the doctrine of equitable title to situations where a corporate parent exercises control over a patentee-subsidiary. Generally, remedies in equity are created in order to avoid unfair results. There is nothing unfair about a corporate subsidiary owning title to a patent, or a corporate parent exercising substantial control over its subsidiary. Furthermore, it is not clear how far such an equitable right would extend and how it would be exercised—surely not every corporate parent has an equitable title to patents held by every corporate subsidiary. Perhaps most importantly, extending the doctrine in such circumstances directly contradicts the statutory requirement that assignment of patent rights must be by an 'instrument in writing.*' See 35 U.S.C. § 261.*

6. *In particular, every judicial opinion that Professor Chisum independently identified involved an actual and affirmative transfer of patent rights from one entity to another. These opinions include:*

6.1 Schwendimann *v.* Arkwright Advanced Coating, Inc.*, 959 F.3d 1065, 1069 (Fed. Cir. 2020) (Chisum Statement at paragraph 16) concerned a written assignment.*

6.2 Dalzell *v.* Dueber Watch-Case Mfg. Co.*, 149 U.S. 315, 320 (1895) (Chisum Statement at paragraphs 19, 24) involved an '*oral agreement for the sale and assignment*' of patent rights.*

6.3 Dickman *v. Vollmer, 303 Wis. 241, 244 (Wis. Ct. App. 2007) (Chisum Statement at paragraph 23) explained '*that the parties orally agreed to assign the patent.*'*

6.4 SourceProse Corp. *v.* RPX Corp.*, 2017 WL 373065, at *1 (N.D. Cal. 2017) (Chisum Statement at 24) pertained to '*an oral agreement for the sales of patents.*'*

6.5 Board of Trustees of the Leland Stanford Junior University *v.* Roche Molecular Sys.*, 563 U.S. 776 (2011) involved an inventor who executed written assignment agreements with two different enterprises.*

6.6 Arachnid, Inc. *v.* Merit Industries, Inc.*, 939 F.2d 1574, 1576 (Fed. Cir. 1991) (Chisum Statement at paragraph 39) addressed a written assignment.*

7. *None of these decisions supports the contention that related corporate entities somehow passively possess an ownership interest in each other's patents.*

SPECIFIC OBSERVATIONS

8. *In paragraph 14 of his Statement, Professor Chisum states that I have not previously cited any judicial opinion that rejected, based on federal law, any state-based ownership of patent rights. I will do so now, noting that some of the following cases are themselves cited in Chisum on Patents. One such case is* Ager *v.* Murray*, 105 U.S. 126 (1891)*[sic ?1881]*, a US Supreme Court decision of even older vintage than Dalzell, that Professor Chisum identifies in Section 9300 of his treatise. There, the Court affirmed the ruling of the Supreme Court of the District of Columbia that a judgment creditor could not seize a debtor's federally granted patent through resort to state law. The Court explained that '[t]*here is nothing in any act of Congress, or in the nature of the rights themselves, to give them locality anywhere, so as to subject them to the process of courts having jurisdiction limited by the lines of States and districts.*' Id. at 130 (citing* Stevens *v.* Gladding*, 58 U.S. 447 (1854)). Although the Court suggested that the state court might be able to compel a written assignment to the debtor, consistent with federal law now housed in Section 261 of the Patent Act, the Court concluded that state law could not be used to transfer ownership of patent rights to settle a money judgment. See also* McClaskey *v.* Harbison-Walker Refractories Co.*, 138 F.2d 493 (3d Cir. 1943) (assessing whether a sheriff's sale of a patent seized under Pennsylvania law complied with R.S. 4898, the predecessor of Section 261).*

9. *Another issue where federal law dominates is the determination of inventorship. '*The federal Patent Act leaves no room for states to supplement the national standard for inventorship.*'*

University of Colorado Foundation, Inc. *v.* American Cyanamid Co.*, 196 F.3d 1366, 1372 (Fed. Cir. 1999). And under US law, the inventors are deemed the initial owners of an invention, patent application, or patent. See* Beech Aircraft Corp. *v.* EDO Corp.*, 990 F.2d 1237, 1248 (Fed. Cir. 1993) (*'At the heart of any ownership analysis lies the question of who first invented the subject matter at issue, because the patent right initially vests in the inventor who may then, barring any restrictions to the contrary, transfer that right to another, and so forth.*'). See also* In re CFLC, Inc.*, 89 F.3d 673, 679 (9th Cir. 1996) (*'[F]ederal law governs the assignability of patent licenses because of the conflict between federal patent policy and state laws, such as California's, that would allow assignability.*');* FASA Corp. *v.* Playmates Toys, Inc.*, 892 F. Supp. 1061, 1064, 1068 (N.D. Ill. 1995) (ruling that federal law deems unenforceable a contractual covenant requiring '*an inventor to waive all rights to the invention" due to the "public policies underlying the . . . patent laws.*').*

10. *In paragraph 15 of the Chisum Statement, Professor Chisum states that I '*postulate that there is, or should be, for 'policy' reasons, a 'uniform' approach to 'corporate structure' . . . *.' While I certainly believe that innovation policy supports current US law as I have presented it to this court, I have not relied merely upon policy arguments. To the contrary, I have cited numerous judicial opinions and other authorities that consistently refuse to recognize equitable title in circumstances analogous to this case. By contrast, Professor Chisum has not cited even a single reference–not one authoritative source, commentator, or even his own treatise—that propounds a contrary position.*

11. *Professor Chisum takes great stock in the venerable* Dalzell *case, but like the other judicial opinions he cites,* Dalzell *involved an affirmative act that transferred ownership—namely a putative oral assignment by an employee who was hired to invent. As a result, I continue to believe that Dalzell lacks pertinence to the current matter. Nonetheless, Professor Chisum asserts in paragraph 20 of his Statement that '[c]*onsistent with Dalzell, Section 261 has never been applied in a case involving a dispute over ownership of a patent priority right (as opposed to ownership for purposes of standing to sue for infringement of a patent).*' He repeats this assertion in paragraph 31 of his Statement. These opinions are plainly incorrect, as indicated by a judicial opinion that Professor Chisum cited with approval in his treatise.*

12. *In* Hewett *v.* Samonsite Corp.*, 507 P.2d 1119 (Colo. App. 1973), the Colorado Court of Appeals (a state court of second instance) applied Section 261 immediately after recognizing the impact of Dalzell. There, Hewett had been employed by Samsonite in a non-inventive capacity. Hewett nonetheless developed several inventions that were later patented. At issue was whether several releases signed by Hewett conveyed ownership of the patents to Samsonite. The Court of Appeals concluded, id. at 1122:*

> *As stated in Dalzell v. Dueber Watch Case Manufacturing Co., Supra, an employer is not entitled to a conveyance of patents obtained for inventions made by an employee in the absence of an express agreement.*

35 U.S.C. §261 provides that patent applications, patents, or any interest therein are assignable 'by an instrument in writing.' Patents and rights in patents are incorporeal personal property. Patterson v. Kentucky, 97 U.S. 501, 24 L.Ed. 1115. An instrument which is claimed to be an assignment of a patent right must adequately express an intention to transfer ownership of the patent right. United States v. Krasnov, D.C., 143 F.Supp. 184. Therefore, the releases did not affect any change in the ownership right between the parties. Hewett still retains his original interests in the inventions and subsequent patents, and Samsonite continues to hold its shop rights thereto.

13. Hewett *v.* Samonsite Corp. *had nothing to do with standing. Rather, the parties disputed the ownership of Hewett's inventions and the patents covering those inventions. And in this context, after recognizing Dalzell and applying Section 261, the state court held that any instrument asserting to assign patents must do so with clarity.*

14. *Professor Chisum referenced* Hewett *v* Samsonite Corp. *with approval in section 22.03 of Chisum on Patents. I agree with him that* Hewett *v.* Samsonite Corp. *correctly reflects US*

law, particularly as it applies Section 261 to an ownership dispute without regard to the law of standing; and also in its insistence that the ownership of patent rights must be expressly transferred in an unambiguous manner. Amongst other state court decisions, Bennett *v.* American Electric Power Service Corp.*, 2001 WL 1136150 at *4 (Ohio App. 2001) is to similar effect.*

15. *Numerous opinions from the federal courts have also applied Section 261 in cases addressing the ownership of patents even though standing is not at issue. See,* e.g., C.R. Bard, Inc. *v.* Medical Components, Inc.*, 2021 WL 2873802, at *2 (D. Utah 2021) (addressing ownership and citing Section 261 for the proposition that a patent assignment must be in writing);* Yufa *v.* TSI Inc.*, 2018 WL 3956489, at *5-6 (N.D. Cal. 2018) (interpreting Section 261 with respect to a receivership); S3* Graphics Co. *v.* ATI Techs., ULC*, 2015 WL 7307241, at *9 (D.Del. 2015) (analyzing assignments for compliance with Section 261);* McClaskey *v.* Harbison-Walker Refractories Co.*, supra. These and other judicial opinions reveal that Section 261 is hardly limited to matters of standing. Rather, Section 261 speaks broadly towards the controlling requirements to transfer title.*

16. *Paragraph 26 of the Chisum Statement states that 'Section 118, in both its earlier and later form, represent a recognition in the federal patent statutes of the established general principle that there can be a 'proprietary' interest, i.e., ownership, in an invention and patent priority rights beyond those already perfected by a written assignment complying with the federal statutes (i.e., Section 261).' I agree with Professor Chisum that Section 118 identified circumstances where one other than the inventor may file a patent application at the USPTO. However, I disagree with his view that Section 118, as it was then framed, afforded an expansive ability for individuals and enterprises to assert equitable ownership and hence file patent applications at the USPTO. Section 118 on its face applied only when inventors were absent or recalcitrant. Professor Chisum's problematic view would render the relevant, predecessor version of Section 118 superfluous, and further suggests that the US Congress need not have bothered to amend that statue in 2011 to permit assignee filing at the USPTO.*

17. *In paragraph 27 of his Statement, Professor Chisum says that I have incorrectly stated that* 'federal law governs the way in which an assignment of patent rights (including the right to claim priority) can be made.' *This account should be contrasted with the statement in Section 22.01 of the Chisum on Patents treatise that the federal* 'patent statutes . . . provide that both patents and patent applications shall be 'assignable in law by an instrument in writing.'' *Likewise, in* Site Microsurgical Systems Inc. *v.* Cooper Companies Inc.*, 797 F.Supp. 333, 335 n.2 (D.Del. 1992), the federal court explained (with emphasis added):*

> *The patent laws specifically provide for the transfer of rights. 35 U.S.C. § 261. Patent rights can be transferred either by assignment or by license. An assignment will be deemed to be a matter of federal patent law whereas a license will normally be governed by state- based contract law. A patent owner can either assign his/her entire interest or assign an undivided portion, making the patentee and the assignees joint owners of the whole interest secured by the patent.*

18. *The Delaware federal court then cited to D. Chisum, Patents: A Treatise on the Law of Patentability, Validity and Infringement § 21.03[2][a] (MB 1991). In Section 22.01 of his treatise, in footnote 3, Professor Chisum references* Site Microsurgical *with approval, reprints the text quoted above, and further indicates that his treatise was cited in that opinion. In my professional opinion, the position taken in* Site Microsurgical *and in Chisum on Patents accurately reflects US law.*

19. *In paragraph 46 of his Statement, Professor Chisum considers* Steelcase, Inc. *v.* Smart Technologies, Inc.*, 336 F.Supp.2d 714 (W.D. Mich. 2004) and* Beam Laser Systems, Inc. *v.* Cox Communications, Inc.*, 117 F.Supp.2d 515 (E.D. Va. 2000). According to Professor Chisum, in* Steelcase 'the district court carefully considered the facts and found standing for one subsidiary but not the other.' *In fact, the* Steelcase *court held that the patentee's corporate parent possessed sufficient rights in the asserted patent because it was a sole*

licensee, had been affirmatively granted exclusive rights to practice the patented invention, and had been affirmatively granted the right to enforce the patent. Id. at 718. Importantly for this matter, the Steelcase *court expressly rejected the notion that common corporate ownership, absent this sort of affirmative transfer, sufficed to grant equitable title in another enterprise's patent. Id. at 718-19.*

20. *In the same paragraph of his Statement, Professor Chisum encounters difficulties with the holding of* Beam Laser *and is left to assert that the case was wrongly decided. (Chisum Statement at paragraph 46). According to Professor Chisum, had Chief Judge Rebecca Beach Smith followed the line of reasoning that he now advocates, then she would have reached a different outcome. I disagree, as Chief Judge Smith's conclusion that '[o]*wnership of corporate stock does not create equitable title in that corporation's property*' correctly states US law. As I noted earlier,* Beam Laser *has been cited with approval in two different sections of Chisum on Patents.*

21. *Professor Chisum and I agree, as he states in Paragraph 47 of his Statement, that accused infringers often contest standing because it serves as a predicate for maintaining a patent enforcement lawsuit in federal court. However, he objects to my assertion that '[s]*imply because a principle of law is frequently articulated within one context does not suggest that it does not apply equally in a related context.'*' Although Professor Chisum observes that I did not cite any authority for this axiomatic principle, he cites none for his contrary view.*

22. *The proposition that property rights should be orderly and predictable cannot be gainsaid. Nonetheless Professor Chisum seemingly disagrees with it in paragraph 55. In this respect, his opinion conflicts with that of the US Congress and courts, which have repeatedly emphasized that patents should provide public notice of what subject matter is proprietary, who owns the patent, and what the consequences of infringement would be. See, e*.g., Nautilus, Inc. *v.* Biosig Instruments Inc., *572 U.S. 898 (2014);* Festo Corp. *v.* Shoketsu Kinzoku Kabushiki Co., *535 U.S. 722 (2002);* Warner- Jenkinson Co. *v.* Hilton Davis Chem. Co., *520 U.S. 17 (1997). I also wish to direct attention to a recent hearing of the Judiciary Committee of the US Congress pertaining to patent ownership. US Congress, Committee Hearing, Pride in Patent Ownership: The Value of Knowing Who Owns a Patent (19 Oct. 2021) (hearing of the US Senate Committee on the Judiciary, Subcommittee on Intellectual Property) (available at www.judiciary.senate.gov). Participants in this hearing explained the current US law of patent ownership, what steps the USPTO takes to promote clarity of patent ownership, and the significant ramifications that result based upon the use of a patent by a specific patent owner. That the US Senate would recently conduct a public hearing on patent ownership further evidences the fact that it is not merely a technical or trivial matter under US law.*

23. *In paragraph 56 of his Statement, Professor Chisum asserts that the USPTO 'does not resolve disputes about ownership' and cites to his treatise. This statement is plainly incorrect, as any reader of Chisum on Patents would discern. As Professor Chisum explains in the very section that he cites, Section 11.20[2][a][ii):*

> *[R]*ecognition of an assignee's right to prosecute forces [USPTOJ [*sic*] to resolve some disputes between inventors and parlies who claim to be assignees. Problems have arisen during prosecution of assigned applications when an assignor-inventor did not approve of an assignee's actions or there are joint inventors and separate assignees.

CONCLUSION

24. *Two consistently stated principles of US law are worth noting for purposes of this litigation.*

24.1 *One is that 'more than a century of corporate law' in the United States holds that a parent corporation does not own the assets of its subsidiaries.* United States *v.* Bennett, *621 F.3d 1131, 1136 (9th Cir. 2010) (further observing that in '1959, the Delaware Supreme Court rejected an argument-much like that presented here-that a parent corporation owns its wholly-owned subsidiary's assets. See* Buechner *v.* Farbenfabriken Bayer*, 154 A.2d 684, 686 (Del.1959).').*

24.2 *The other is that the US Supreme Court has repeatedly decried the creation of special rules, outside the mainstream of US law and equitable practice, for patent cases. See,* e.g., eBay Inc. *v.* MercExchange, LLC*, 547 U.S. 388 (2006) (overturning lower court decisions that departed from mainstream equitable principles).*

25. *Professor Chisum views the priority issue before this court as a knotty one, but in truth it is straightforward. The case law ruling that corporate parents do not possess equitable title in patents owned by their subsidiaries is overwhelming. Many dozens of US judicial opinions reject this theory of ownership, and Professor Chisum does not cite a single source that says otherwise. As a result, this court has no reason to proceed to Delaware because the case law I have cited is dispositive of the matter.*"

APPENDIX 8

Abridged Written Evidence of Ms Sandra Leung

"*9. When I refer to the 'relevant time' in this Witness Statement, I mean the time period beginning with the time BMS acquired DuPont Pharmaceuticals Company in October 2, 2001 through September 17, 2002, which I understand is the date that international application PCT/US02/29491 was filed in the name of its inventors (for the US part) and BMS Co (for ex-US parts), claiming priority from US Application No. 60/324,165 and seeking registration as a European Patent among others (and which resulted in EP 1 427 415 and ultimately the Patent in suit).*

My Views on the Expert Statement of Dr. Jacobus C. Rasser

10. I have been asked to review the Rasser Statement and to provide my views of the statements and opinions expressed therein based on my background and experience.

11. As an initial matter, it is my view that Dr. Rasser's statements with regard to how Procter & Gamble ('P&G') may have been structured, how P&G may have handled IP within its corporate structure, or what was 'very important at P&G' are irrelevant to the situation at BMS. Based on my background and experience, it is my understanding that different corporations may be structured differently, may have different ways of handling IP within their corporate structure, and may have different corporate policies and practices. Accordingly, while Dr. Rasser stated that '[a] very important point at P&G was that all of the IP was owned and held by a specific entity, no matter where the invention was made or where the trademark was filed' and '[i]n the case of P&G it was all owned by the parent company,' such are not, and were not during the relevant time, relevant to BMS given its corporate structure and how decisions with respect to IP were and are made.

12. BMS was in the relevant time, and has been since, organized with a centralized corporate structure in which BMS Co is the ultimate parent company of the Bristol-Myers Squibb group of companies. As a result of this centralized corporate structure, all IP-regardless of which of BMS Co's wholly-owned subsidiaries held legal title-is and was held for the ultimate benefit of BMS Co. BMS Co had in the relevant time, and has had since, control over how the IP assets and associated IP rights of its wholly-owned subsidiaries are held. In this regard, BMS had in the relevant time, and has since, a single IP department for all of BMS, which is led by an officer of BMS Co. and which, at the relevant time and through today, managed the IP assets of BMS for the ultimate benefit of BMS Co. In particular, this IP department in the relevant time, and since then, exercised ultimate control over the location and disposition of all IP, including for any IP rights, including the rights to claim priority, held by any BMS companies.

13. In addition, at BMS it was common practice at the relevant time and through today that when BMS acquires another company, legal title to the other company's IP is left in place with the acquired subsidiary, which is wholly-owned, directly or indirectly, by BMS Co, rather than having such legal title assigned to BMS Co. In such circumstances, because the subsidiary was wholly-owned by BMS Co, it was not, and is not, relevant to BMS whether or not the legal title to the IP was actually held by BMS Co. This is because BMS Co, as the ultimate parent company, has, and had during the relevant time, the ability to exercise ultimate control over any IP rights regardless of which of its wholly- owned subsidiaries may hold legal title to the IP.

14. Decisions as to ownership of such acquired IP are, and at the relevant time were, made by BMS Co, and the Corporate Secretary group that I led in 2002 is and was involved in those decisions along with the IP department discussed above. This is what was done in the case of the DuPont Pharma acquisition. In particular, following the acquisition of DuPont Pharma by BMS Co, BMS Co made the decision to leave the IP assets held by DuPont Pharma with that entity, which was wholly-owned by BMS Co, and BMS Co merely changed

the name of that entity to Bristol-Myers Squibb Pharma Company ('BMS Pharma'). BMS Co, nonetheless, as the ultimate parent company, exercised control over, and was the beneficial or equitable owner of, all IP rights held by BMS Pharma.

15. *It should be noted that, as was explained in the press release attached hereto as Appendix 1, BMS Co paid $7.8 billion in cash for DuPont Pharma, and a primary reason that BMS Co paid such money to acquire DuPont Pharma was to strengthen BMS Co's virology and cardiovascular franchises, R&D pipeline and discovery efforts. In particular, as was expressed at the time in Appendix 1: with this acquisition, Bristol-Myers Squibb gains several important in-line products, including Sustiva™ (efavirenz), the leading non-nucleoside reverse transcriptase inhibitor for the treatment of HIV/AIDS; Coumadin® (warfarin sodium tablets, USP), a widely used oral blood anticoagulant; and Cardiolite® (Kit for the preparation of Technetium Tc99m Sestamibi for Injection), a leading cardiovascular medical imaging agent. The company also gains a rich and productive R&D pipeline that contains a number of early compounds with novel mechanisms that have the potential to be first in class and blockbusters. The pipeline includes compounds in five therapeutic areas – virology, cardiovascular diseases, inflammatory diseases, cancer and disorders of the central nervous system.*

16. *Since a primary purpose of BMS Co's acquisition of DuPont Pharma was to strengthen its virology and cardiovascular franchises through the acquisition of those in-line products, R&D pipeline, and other assets of DuPont Pharma (collectively, the 'Dupont Pharma Assets'), BMS Co would necessarily need to be in control of the IP rights, in particular the patent rights, that protect those DuPont Pharma assets. Thus, it would only have made sense to, and BMS Co would have only agreed to, house the patents protecting the DuPont Pharma Assets in BMS Pharma if BMS Co had the beneficial/equitable ownership of, and the ability to control, those patents, which was in fact the case at the relevant time. In particular, during the relevant time, BMS Pharma was a wholly-owned subsidiary ofBMS Co and was subject to its control and direction. Further, BMS Co was the beneficial and equitable owner of any IP rights held by BMS Pharma.*

17. *How we handled the DuPont Pharma acquisition is consistent with BMS's longstanding general policy and practice that continues today of leaving all of the acquired IP in a wholly-owned subsidiary for the benefit of BMS Co. In other words, when BMS Co acquires an entity, we generally keep the assets of that entity in that entity, but it is held for the ultimate benefit of BMS Co, and BMS Co wholly owns that entity and has the right and ability to control that IP. This policy makes sense given the way BMS is and was at the relevant time structured and operated.*

18. *I have reviewed the Witness Statement of Paul Golian, and it is consistent with my recollection and understanding of the circumstances surrounding the DuPont Pharma acquisition and BMS's policies and practices during the relevant time.*

19. *Likewise, I have reviewed the email dated October 29, 2001, which forwards an email dated October 24, 2001 to a group of recipients, including myself. The October 24, 2001 email sets out recommendations, which appear to have initially come from Margaret Yonco-Haines, who worked in the BMS Co tax department, for the legal entity registration of various IP assets of the DuPont Pharmaceuticals business. In relation to the patents and trademarks of the pharmaceutical business, the recommended course of action is stated as follows:*

> (I) *<u>Patents and trademarks related to the Pharmaceutical business</u> Maintain legal ownership in Bristol-Myers Squibb Pharma Company (formerly DPC). We believe that this is the entity where they currently reside, so this should involve only a name change. New patents and trademarks m the name of Bristol-Myers Squibb Company.*

20. *This recommendation in this email is in accordance with the decision-making and general policy and practice of BMS Co described above whereby acquired IP is often left in the acquired wholly-owned subsidiary. Specifically, legal ownership of BMS Pharma's IP assets*

remained with DuPont Pharmaceuticals Company, and the name of that entity was later changed to the new name, Bristol-Myers Squibb Pharma Company. Again, BMS Co. was the ultimate parent company of BMS Pharma and was the beneficial owner of such IP assets and controlled how IP rights of its wholly-owned subsidiaries were held. There was no need for BMS Co. to place the IP assets acquired from DuPont in BMS Co. at any particular time because it maintained control over the IP at all times and could decide to have BMS Pharma assign those IP assets to it (or any other entity) whenever it wished to do so when it served a business purpose, as it did so here."

APPENDIX 9

Abridged Written Evidence of Professor Morrissey

Statement #1 of 2

"***The identity of the skilled person/team***

20. McCann FitzGerald LLP have explained to me that the Patent is to be read through the eyes of the notional person skilled in the art. I have been told that this is someone who is likely to have a practical interest in the subject matter of the invention and has the practical knowledge and experience of the kind of work in which the invention is to be used. He or she lacks inventive capacity but is taken to have the common general knowledge of those working in the field to which the invention relates. I have also been told that the skilled person can be a team.

21. Paragraph [0001] of the Patent states that the invention relates generally to 'lactam-containing compounds and derivatives thereof which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment of thromboembolic disorders.' Protease enzymes are enzymes that cleave peptide bonds in proteins. Serine proteases are enzymes that cleave peptide bonds in proteins, in which serine serves as the nucleophilic amino acid at the active site. Factor Xa is a serine protease. Compounds designed to block serine proteases from working effectively are called serine protease inhibitors.

22. I believe that the Patent would be of interest to a skilled team involved in the development of factor Xa inhibitors. I would expect the team to include expertise in the fields of medicinal chemistry, biochemistry and pharmacology (including pharmacokinetics).

23. The majority of the disclosure in the Patent relates to the development and synthesis of new chemical structures which would primarily be of interest to the medicinal chemist. However, as the biological target is factor Xa and the Patent includes descriptions of the methods of evaluating the efficacy of factor Xa inhibitors, I believe that a biochemist with experience in the field of thrombosis and hematology and a detailed knowledge of the coagulation cascade would also be part of the skilled team. The role of the biochemist would include performing and reviewing the results of in vitro tests (such as the effects of the factor Xa inhibitors on clotting tests using citrated human plasma[1], as well as effects of the factor Xa inhibitors on the enzymatic activity of purified factor Xa and related serine proteases) and in vivo tests (such as the AV shunt model).

24. In my opinion, the biochemist would have a background in biology and would have gained an undergraduate degree and either a PhD in biology or biochemistry and two years' experience in a lab or alternatively five years' experience in a lab focusing on research in the field of thrombosis.

25. They would have a detailed working knowledge of the coagulation cascade, including the role of factor Xa and would understand why factor Xa was a key therapeutic target at the priority date. The biochemist would have a good working knowledge of the standard in vitro assays used to test serine protease inhibitors and would be able to collate and interpret the results from these assays. They would also be familiar with standard animal models used to test serine protease inhibitors that targeted blood clotting enzymes, and which were promising potential clinical candidates.

26. The rest of this witness statement is written from the perspective of the person described in paragraphs 24 and 25 above, who I refer to as 'the biochemist'.

27. McCann FitzGerald LLP have explained to me that what is important is not my own personal knowledge and views in relation to the issues addressed in this witness statement but those of the relevant skilled person. I believe that, except where I have indicated otherwise, the

knowledge and views expressed in this witness statement would have been representative of the views of those working in the field in September 2001.

Common general knowledge of the biochemist

28. It has been explained to me that common general knowledge ("CGK") refers to information that is generally known and generally accepted by the bulk of those working in a particular field as a reliable basis for further work at the relevant time. I have been told that CGK is not limited to the material that the skilled person has memorised but also includes information that is known to exist and would be referred to as a matter of course, if necessary. I also understand that CGK is typically reflected in textbooks and review articles which were widely read or consulted at the time, or shortly afterwards.

29. Except where I have stated otherwise, I believe that the information set out below would have been part of the CGK of the biochemist working in the blood coagulation field in September 2001. Where I use the present tense, it should be understood that my account is of the CGK at that date. Where appropriate, I have provided references to important scientific articles and reviews.

Sources of CGK

30. At the priority date of the Patent, the CGK of the biochemist would have been reflected in various publications, including textbooks such as:

a. Hemostasis and Thrombosis: Basic Principles and Clinical Practice, 4th Edition, Colman, Hirsh, Marder, Clowes, & George, eds. (Lippincott Williams & Wilkins, Philadelphia), 2000; and

b. Modern Hematology - Biology and Clinical Management, Munker, Hiller and Paquette (Humana Press Inc.), 2000.

31. The biochemist would also have been interested in high quality review articles in journals. At this time, I would expect the biochemist to have a monthly subscription to some journals and to use services that regularly delivered copies of the table of contents of scientific journals, as well as to use both print-based abstract searches and online search services such as PubMed to flag up any other articles of interest. Serine protease inhibitors were a topic of interest in 2001 and there were already a number of articles and discussions on the topic by September 2001. The journals I would expect the biochemist to be familiar with and to be particularly interested in reading articles from include:

a. Arteriosclerosis, Thrombosis and Vascular Biology;
b. Blood;
c. Circulation; and
d. Thrombosis & Haemostasis.

32. There were a number of conferences in the field of thrombosis with attendees from a mixture of disciplines across the research and clinical fields (e.g., hematologists, cardiologists, biologists, biochemists etc.). I would expect the biochemist to attend at least some of these conferences on a regular basis. Amongst the most important conferences in this field are:

a. The meeting of the International Society on Thrombosis and Haemostasis (which, at that time, was held every two years);
b. Annual meeting of the American Heart Association;
c. Annual meeting of the American Society for Hematology; and
d. 'Hemostasis' meeting by the Gordon Research Conferences (held every two years).

Thrombosis

33. *Thrombosis is the formation of an unwanted blood clot (termed a "thrombus") inside a blood vessel. Thrombosis is one of the leading causes of disability and death in the world. If blood clots form in arteries and block the flow of blood, this can lead to a heart attack, stroke, or lower limb gangrene requiring amputation. Blood clots that form in the deep veins of the legs, known as deep-vein thrombosis ('DVT'), can break off, travel round the circulatory system (embolize) and lodge in an artery of the lungs, causing a pulmonary embolism ('PE'). A clot, or a piece of the clot, that breaks free and begins to travel around the body is known as an embolus.*

34. *'Thrombotic disorder' usually refers to a range of disease states in which thrombi form inside blood vessels, which pose the threat of obstructing blood circulation. The term 'thromboembolic disorder' can be used as a general term that encompasses both thrombi that form in place as well as thrombi that have broken loose and lodged in a blood vessel in another part of the circulatory system.*

The coagulation cascade

35. *In a healthy human being, clotting processes prevent excessive bleeding and participate in repair of damaged blood vessels. If the system is functioning properly, blood clots that form at the sites of blood vessel injury seal the leaks and are then removed later on. Hemostasis is the mechanism that leads to cessation of bleeding from a blood vessel. It is a process that involves multiple interlinked steps culminating in the formation of a "hemostatic plug" that closes up the damaged site of the blood vessel, controlling the bleeding. There are two stages of hemostasis:*

    a. Primary hemostasis refers to platelet aggregation and platelet plug formation. Platelets circulate in the blood in inactive form. The platelets become activated, for example, by coming into contact with collagen on the vessel wall (exposed by damage), or by the action of thrombin. Activation causes platelets to clump together and adhere to the site of injury and to each other, plugging the injury.
    b. Secondary hemostasis refers to the process in which fibrin is formed to stabilize the loose platelet clot formed in primary hemostasis. Secondary hemostasis involves a cascade of enzymatic reactions (the "coagulation cascade") that ultimately results in the conversion of fibrinogen to fibrin monomers. Fibrin monomers then self- associate into fibrin strands which are then cross-linked into insoluble strands that serve to stabilize the loose platelet clot formed in primary hemostasis.

36. *The coagulation cascade describes the process by which the blood clots. As explained above, the blood can clot in normal hemostasis or in thromboembolic disorders. It was well known that thrombotic/thromboembolic disorders could be treated by reducing blood clotting through inhibiting the coagulation cascade.*

37. *The enzymes involved in the coagulation cascade are termed "factors." The coagulation cascade can be considered as a series of activation steps, each of which involves a proteolytic conversion of a zymogen (the inactive precursor of an enzyme, in this case the inactive form of the clotting factor) to the corresponding active serine protease (an enzyme capable of cutting one or more peptide bonds in certain proteins; it is the activated form of the clotting factor). The active form of each clotting factor converts the inactive form of the next factor in the coagulation cascade to its active form (although some factors have multiple roles). The 'a' in the name of a factor indicates the factor in its active form.*

38. *There are two main pathways for triggering the coagulation cascade: the intrinsic (or contact) pathway and the extrinsic (or tissue factor) pathway. These merge to form a third pathway: the common pathway. Figure 1 below is taken from a review article which my lab published in 2015 [2] but it reflects the biochemist's understanding of the coagulation cascade in September 2001. It shows each of the three pathways.*

    [Diagram not in judgment]

39. *The intrinsic pathway is so-called because all the necessary components of this pathway are*

in the plasma and no external source is required to trigger this pathway (unlike the extrinsic pathway that, as explained below, requires exposure to tissue factor for triggering). The intrinsic pathway only plays a limited role in hemostasis, but can be triggered when blood comes into contact with certain negatively charged surfaces, such as glass. The intrinsic pathway ultimately results in the generation of factor XIa, which then converts factor IX to factor IXa. Most of the intrinsic pathway is dispensable for normal hemostasis, since individuals lacking most of the proteins in this pathway (such as factor XII or prekallikrein) have no bleeding disorders. However, factor XI is involved in normal hemostasis, as individuals with factor XI deficiency are prone to bleeding. Today (in 2022), current thinking is that, under some circumstances, thrombin feeds back to activate factor XI to create sustained thrombin generation (not shown in Figure 1 above).

40. *Figure 2, below, is a simplified diagram of the extrinsic and common pathways (taken from page 90 of Chapter 5, which I wrote, in Hemostasis and Thrombosis: Basic Principles and Clinical Practice, 4th Edition (2000)[3], which is at Appendix JHM2). The intrinsic pathway which is discussed above is not included in this diagram, because it only plays a limited role in hemostasis.*

[Diagram not in judgment]

41. *In the above Figure 2, the extrinsic (or tissue factor) pathway triggers the coagulation cascade at two steps (labelled (1) and (2)). The extrinsic pathway is activated when the blood comes into contact with tissue factor (TF). Tissue factor is present on the surface of a variety of cell types located outside the vascular system, but under normal conditions tissue factor is not present within the vascular system (i.e., it is not normally expressed by cells in direct contact with plasma). The extrinsic pathway is therefore activated by external trauma causing a vascular injury and exposing plasma to tissue factor. Tissue factor binds to factor VII (resulting in it being converted to factor VIIa). There are also trace amounts of factor VIIa circulating in the plasma at all times and tissue factor can also bind to this. The complex of tissue factor and factor VIIa initiates the coagulation cascade by activating either factor IX (the step labelled (1) in Figure 2) or factor X (the step labelled (2) in Figure 2). Both steps (1) and (2) lead to the formation of factor Xa.*
42. *Factors Xa and Va assemble on a phospholipid surface (PL). Factor Xa then binds to its protein cofactor (factor Va) to form a complex (often termed 'prothrombinase') which catalyses the conversion of prothrombin to thrombin.*
43. *Thrombin then converts fibrinogen to fibrin. Fibrin polymerises to form a gel, or fibrin mesh which binds platelets together forming a clot and also contributes to their attachment to the vessel wall. The fibrin mesh makes the aggregates of platelets formed in primary hemostasis more stable, particularly for larger injuries.*

Inhibition of Coagulation

44. *By 2001, three main classes of anticoagulant drugs had been commercialised or were under development: (i) vitamin K antagonists; (ii) heparins; and (iii) serine protease inhibitors. Anticoagulant drugs slow down or inhibit clot formation by interfering with one or more of the enzymes involved in the coagulation cascade.*
45. *There has to be a balance between anticoagulant forces in the blood and procoagulant forces (which cause clotting). If the anticoagulant effect is too strong, the individual risks excessive bleeding because a clot does not form when it should. In contrast, if the procoagulant effect is too strong there is a risk of thrombotic disorders (clots forming inside a blood vessel).*
46. *Anticoagulants are usually prescribed when either the patient already has a blood clot (with the aim of stopping the clot increasing in size and embolising thus giving the body a chance to break down the clot itself over time) or the patient is at high risk of developing a blood clot (with the aim of preventing a blood clot forming in the first place).*

Vitamin K antagonists

47. *Vitamin K antagonists ('VKAs') block the processing of vitamin K in the liver. VKAs have been in use since the 1950s and one very well-known example is warfarin.*

48. *A number of coagulation factors are synthesized in the liver using vitamin K, such as prothrombin and factors VII, IX and X. Therefore, by blocking vitamin K, the synthesis and proper post-translation modification of these vitamin K-dependent proteins is slowed down. Administration of VKAs results in the reduction in the levels of active prothrombin and factors VII, IX and X which, as I have explained, play crucial roles in the coagulation cascade. VKAs also inhibit the proper post-translational modification of three anticoagulant proteins (proteins C, S and Z), affecting their Ca^{2+} and membrane binding capabilities (preventing enzyme complexes from forming).*

49. *VKAs are often referred to as being indirect anticoagulants as they have no intrinsic anticoagulant activity themselves, but have an indirect effect on the coagulation cascade. In 2001, VKAs were the most widely used anticoagulants (and indeed were the only approved oral anticoagulants available at that time).*

50. *However, there are a number of very significant disadvantages with VKAs which were well-known at the priority date:*

    a. the therapeutic dose varies from patient to patient and can even vary over time for the same patient. It is therefore necessary to perform recurring blood tests to measure the effect of warfarin on a patient, to identify the appropriate dose and to adjust the dose as necessary. The test result is referred to as the patient's International Normalised Ratio ('INR');

    b. VKAs have a narrow therapeutic window (i.e. the range of doses of the drug which can treat a disease effectively without being toxic or causing harmful side effects) and there are huge risks to the patient if they fall outside the narrow therapeutic window (i.e., an increased risk of blood clots or an increased risk of bleeding);

    c. VKAs are subject to many drug-drug and drug-food interactions. As a result, even after the optimal dose is identified for a particular patient, it is necessary to continue to monitor their INR on a regular basis to ensure that the dose remains within the therapeutic window;

    d. VKAs can lead to an increased risk of calcification (a build-up of calcium deposits) of the patient's arteries which can result in adverse clinical effects; and

    e. VKAs have a slow onset of action and their high oral bioavailability and long half- life means that their anticoagulant action continues for several days after treatment stops.

51. *VKA treatment was time consuming and costly, inconvenient for patients and still left patients with a significant risk of bleeding side effects. As a result, there was a desire to develop other anticoagulants.*

Heparins

52. *Heparin was another anticoagulant that had been in widespread use for decades by 2001. There are two main types of heparin drugs: (i) unfractionated heparin ("UFH"), also known as standard heparin; and (ii) low-molecular-weight-heparins ("LMWH"). Heparin must be administered subcutaneously or intravenously and so is more difficult to administer than VKAs. Heparin takes effect more quickly than VKAs, so it is usually given in clinical situations where an immediate effect is required. It is also possible to reverse the effects of UFH quickly using a reversal agent, protamine sulfate.*

53. *Heparin is naturally occurring and acts by binding to the enzyme inhibitor Antithrombin III ('AT'[4]). A deficiency in AT predisposes a person to thrombotic disorders. Heparin produces its major anticoagulant effect by inactivating thrombin and factor Xa through an AT-dependent mechanism. The catalytic-site serine of thrombin reacts with AT to form an inactive complex which prevents the thrombin from activating fibrin. Heparin is therefore an indirect inhibitor of thrombin and factor Xa.*

54. *UFH is a sulfated polysaccharide with a molecular weight range of 3000 to 30 000 Da (mean,*

15 000 Da). UFH suffers from the following drawbacks:

a. *it has to be administered by injection;*
b. *it does not effectively inhibit prothrombinase activity;*
c. *the size of the AT-heparin complex renders it incapable of inhibiting thrombin once it is in a complex with fibrin in a growing thrombus i.e., it has a very limited ability to access clot-bound clotting enzymes;*
d. *it gives widely varying responses and a lack of predictability, requiring continuous monitoring of the patient;*
e. *around 3% of those treated develop heparin-induced thrombocytopenia ('HIT'), which can be life-threatening; and*
f. *it can result in thrombotic rebound phenomenon after treatment is stopped.*

55. *LMWHs were developed to try and overcome some of the problems associated with UFH. LMWHs are fragments of UFH produced by controlled enzymatic or chemical depolymerization processes that yield chains with a mean molecular weight of about 5000 Da (i.e., approximately one-third the size of UFH). LMWHs were commercially available well before 2001. Unlike UFH which targets both thrombin and factor Xa, LMWH tends to favor factor Xa as a target over thrombin (owing to differences in the mechanism of action).*
56. *LMWH has several advantages over UFH: (i) it allows predictable and well-controlled anticoagulation, with fixed dose administration; (ii) its bioavailability and half-life is good with subcutaneous administration and does not require continuous monitoring; and (iii) patients are at reduced risk of developing HIT. However, the use of LMWH is not superior in every situation and both types of heparin continue to be used in the clinic.*
57. *Another subset of heparins which had been developed by 2001 were the pentasaccharides. These were synthetic heparin fragments with even lower molecular weights than LMWH. By 2001, the best-known of these was "fondaparinux" (also referred to as Org31540 or SR90107A in the literature). Fondaparinux binds to AT in the plasma to have an anticoagulant effect and once bound to AT it only inhibits factor Xa and not thrombin.*
58. *Fondaparinux is discussed in-depth in a March 2001 paper by Turpie et al, in the New England Journal of Medicine (Appendix JHM3), which reports on a phase II clinical trial of fondaparinux and concludes, on page 625, that: 'These findings suggest that selective inhibition of factor Xa by potentiation of the effects of antithrombin may be highly effective in the prevention of venous thromboembolism in patients undergoing total hip replacement, and this prophylactic treatment is associated with less bleeding at a level of protection similar to that of low-molecular-weight-heparins.'*
59. *The significance of the results with fondaparinux was discussed in an Editorial in the same March 2001 edition of the New England Journal of Medicine (see page 673 of Appendix JHM4) which references the Turpie paper and also refers to phase III clinical trials. In the third paragraph, left hand column on page 674, it says: "The superior efficacy of the pentasaccharide [fondaparinux] in this phase 2 dose-finding study has been corroborated by recently completed phase 3 studies in patients undergoing total hip replacement or knee replacement and in patients with hip fracture. The clinical effectiveness of the pentasaccharide [fondaparinux] shows that anti–factor Xa activity alone is sufficient for the prevention of venous thrombosis."*

Serine protease inhibitors

60. *Due to the significant limitations of VKAs and heparins there was substantial interest in finding alternative anticoagulants and, in particular, anticoagulants that could be taken orally. Many of the coagulation factors are serine proteases (with exceptions including TF and factors V, VIII and XIII). Serine protease inhibitors interact with serine protease enzymes and reduce their activity by influencing the binding of substrate and/or the number of reactions the enzyme turns over per unit time.*

61. *By 2001, there was very substantial interest in directly targeting the serine proteases in the coagulation cascade, in particular factor Xa and thrombin, and they were being actively pursued as targets for developing anticoagulants. There was a large volume of literature on the subject and the latest developments were being discussed at conferences. The biochemist would have been following the literature with interest, as indeed I did at that time.*

62. *Due to its proximity in the pathway to the blood clotting event, direct thrombin inhibitors were an early focus of drug discovery efforts to find new anticoagulant medicines. Thrombin had been heavily studied in the 1980s and early 1990s and its crystal structure was reported in 1989.*

63. *However, direct thrombin inhibitors were thought to suffer from a number of potential drawbacks relative to factor Xa inhibitors:*

    a. *Inhibition of the prothrombinase complex (by targeting factor Xa) should prevent the continuing production of thrombin while maintaining a basal level of thrombin activity necessary for primary hemostasis. The prothrombinase complex present at the site of injury is unaffected by direct thrombin inhibitors and so cannot prevent the continuing production of thrombin;*
    b. *Thrombin inhibitors showed a tendency to increase the likelihood of bleeding complications; and*
    c. *Thrombin has both procoagulant actions (including converting fibrinogen into fibrin, activating factor XIII to XIIIa, and activating platelets) and anticoagulant actions (in the presence of thrombomodulin, converting protein C into activated protein C - an important natural anticoagulant in plasma). Given the known pleiotropic effects of thrombin, there was a concern that inhibiting thrombin's enzymatic activity may have in vivo effects that would be difficult to predict.*

64. *Factor Xa was considered to be a promising target with several potential advantages:*

    a. *Both the extrinsic and intrinsic pathways of coagulation culminate in factor Xa activation. Factor Xa then triggers thrombin generation and fibrin formation via the common pathway. Due to its position at the convergence of the two separate pathways and because it catalyzes the conversion of prothrombin to thrombin, factor Xa was understood to play a central and crucial role in the coagulation cascade;*
    b. *Factor Xa inhibitors were predicted to have a lower risk of bleeding than heparin and VKAs and a much wider therapeutic window than direct thrombin inhibitors because they specifically inhibit coagulation without directly affecting platelet function (see page 63 of Appendix JHM5, a 1999 review article by Zhu and Scarborough which appeared in Current Opinion in Cardiovascular, Pulmonary and Renal Investigational Drugs);*
    c. *Compared to thrombin, factor Xa was thought to have fewer functions outside the coagulation cascade and therefore negative side-effects as a consequence of inhibiting factor Xa were hoped to be more limited; and*
    d. *When the clotting process begins, many molecules of factor X are activated and each factor Xa molecule can activate more than one substrate molecule. In fact, it was known in 2001 that one molecule of factor Xa could generate many molecules of thrombin per minute. It was therefore hypothesized that factor Xa inhibition could be a more effective and safer way to prevent blood clot formation than direct thrombin inhibitors as less drug would be needed.*

65. *Appendix JHM6, an article by Robert Leadley which appeared in Current Topics in Medicinal Chemistry in June 2001, addresses the biological background and rationale for targeting factor Xa and would have been of interest to the biochemist. Page 152 explains that factor Xa has been validated as a viable drug target before explaining the rationale for developing factor Xa inhibitors. Leadley goes on to discuss some of the factor Xa inhibitors that were in development, including fondaparinux (ORG31540) which I referred to earlier in my witness statement (see pages 153 and 156 of JHM6 and Table 1 on page 155).*

66. *By 2001, factor Xa was widely accepted to be a promising target for the development of antithrombotic drugs. The biochemist working in the field of thrombosis would have been aware that there was significant interest within the pharmaceutical industry in developing and commercializing small molecule factor Xa inhibitors (see, for example, page 153 of Appendix JHM6: 'Based on the favorable preclinical evidence provided by recombinant forms of naturally occurring fXa inhibitors, many pharmaceutical companies quickly initiated chemistry programs that produced potent and selective small molecule inhibitors of fXa…').*

67. *I looked back at the literature to remind myself of the state of the art in 2001 and I found an article by Spencer and Becker, published in the Current Cardiology Reports in 2000 (Appendix JHM7). I think that this article accurately summarises what was known in the field at that time. Table 2 on page 400 helpfully summarises the stage of development of several synthetic factor Xa inhibitors and shows promising initial results.*

Testing potential anticoagulants

68. *Various in vitro assays could be used to assess the effectiveness of a potential coagulation inhibitor. By 2001, the most commonly used assays to assess potential inhibitors of serine proteases in the coagulation cascade were clotting assays and enzymatic assays using chromogenic substrates.*

69. *A clotting assay would often be done as it is cheap and, using automated coagulometers, the skilled person can carry out large numbers of assays in a short time. There were two very commonly used types of clotting assays: (i) prothrombin time (PT); and (ii) activated prothrombin time (aPTT). Clotting assays measure the time required for citrated plasma to clot after appropriate recalcification and initiation of either the extrinsic (PT) or the intrinsic pathway (aPTT) of the plasmatic coagulation cascade.*

70. *A chromogenic assay was a test which produced a color change if the serine protease under assessment cut an amide bond that linked a short peptide to a chromophore, releasing a free dye that would absorb visible light. For example, the use of a factor Xa substrate in this assay would reveal the presence of factor Xa and the resulting intensity of color can be measured using a spectrophotometer to determine the amount of factor Xa enzymatic activity present. In the presence of a serine protease inhibitor, these data can be used to derive a K_i value[5] which indicates the concentration at which the inhibitor is effective in inhibiting factor Xa. A decrease in the rate of absorbance indicates factor Xa inhibition. A greater decrease in the rate of absorbance indicates greater factor Xa inhibition – hence a low K_i is indicative of an inhibitory effect at a low inhibitor concentration (meaning that the inhibitor has a relatively high in vitro potency). In vitro tests would also be run with other serine proteases to determine selectivity. The skilled person would only need a very small amount of the compound for in vitro testing (i.e., microgram to milligram quantities) assuming that the compound has nanomolar potency.[6]*

71. *The diagram below, which was provided to me by Hogan Lovells in the context of the proceedings before the High Court of England and Wales, represents how a chromogenic assay works in the context of a synthetic substrate being cleaved by factor Xa. The amino acids of the substrate are shown as circles labelled with their abbreviated names and the chromophore is shown as a diamond labelled "pNA". Factor Xa cleaves the bond between the arginine and the chromophore, the chromophore is released as free dye, and this causes the color change in the assay:*

[Diagram not included in Judgment]

72. *It is possible to test thousands of compounds in vitro using high-throughput screens. If in vitro tests showed a candidate to be promising, they would typically be followed with in vivo tests. Initial in vivo tests would usually involve manipulating a blood vessel (damaging it or introducing a substance that triggers clotting) in a subject animal to encourage a clot to form and then measuring the decreased blood flow over time. The animal used in these tests has to be big enough to allow access to the blood vessels and common animal subjects*

include rodents and rabbits but other test subjects could be used.[8]

73. *Another common test was the arterio-venous (AV) shunt model. This involves connecting tubing to an artery of an animal at one end and a vein of the same animal at the other. Blood then flows through the tubing (the shunt) into which a stimulus is introduced to induce thrombosis. Often, a silk thread is placed into a segment of the tubing which triggers the intrinsic pathway of the coagulation cascade. The efficacy of an anticoagulant can be evaluated by measuring the clot formation within a set period of time. The results from this model allow the biochemist to derive an ID_{50} value for the compound (dose which produces 50% inhibition of thrombus formation) which tells the biochemist whether or not the compound being tested has anti-clotting properties.*

74. *The amount of the compound needed to run the AV shunt models depends on a number of factors - e.g., the type and size of animal involved, the number of animals involved etc. If the skilled person had gram quantities of the compound, this would usually be more than enough to run animal studies (in fact less than a gram would usually be sufficient).*

The Patent and the Application

75. *The Application is entitled "Lactam-containing compounds and derivatives thereof as factor Xa inhibitors". A skilled biochemist reading the Application (and the Patent) on 21 September 2001 in light of their CGK would have understood the following.*

76. *Page 1 explains that the invention relates generally to compounds which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, and methods of using the compounds as anticoagulant agents for the treatment of thromboembolic disorders.*

77. *The majority of the Application (and the Patent) concerns the chemical structures of the inhibitors and synthesis of these compounds and these sections would primarily be of interest to the medicinal chemist on the skilled team. However, there are sections of the Application (and the Patent) which would be of interest to the biochemist and I have set these out below.*

78. *Pages 5 and 6 of the Application ([0018] in the Patent) discuss the role of factor Xa in the coagulation cascade. They explain that the major role of activated factor Xa is to generate thrombin and that it links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. As explained above in the section on CGK, this was well-known by September 2001.*

79. *The Application goes on to explain that because one molecule of factor Xa can generate 138 (i.e., many) molecules of thrombin, the inhibition of factor Xa may be more efficient than inhibition of thrombin in interrupting the blood coagulation system. In other words, factor Xa is a good target to try and inhibit. The biochemist would agree that this is a logical reason for targeting factor Xa and indeed, it is one of the reasons that was already well-known and well-documented by September 2001.*

80. *Page 6 of the Application ([0019] of the Patent) sets out a list of the characteristics that a factor Xa inhibitor should have. The biochemist would understand that these are all characteristics that the skilled team would need to pay attention to when developing a factor Xa inhibitor.*

81. *Page 7 of the Application ([0020] to [0026] of the Patent) explains that the compounds of the invention and pharmaceutical compositions containing those compounds are useful as factor Xa inhibitors. The Application states that the invention provides a method for treating thromboembolic disorders by administering to the patient a therapeutically effective dose of one of the compounds of the invention. Page 168, lines 15 – 18, of the Application ([0113] of the Patent) also states that the compounds of the invention are factor Xa inhibitors that are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals.*

82. *Page 168 of the Application ([0113] of the Patent) explains that, in general, a 'thromboembolic disorder' is a circulatory disease caused by blood clots (i.e., diseases involving fibrin formation, platelet activation, and/or platelet aggregation). It is then explained that as used in the Application, the term is intended to include arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart as well as specific*

disorders selected from a comprehensive list.

83. *The Application then goes on to set out how the effectiveness of the compounds of the invention could be determined. On page 169, starting at line 22 ([0114] of the Patent) the details of an assay to measure the compounds' effectiveness in the inhibition of factor Xa using purified human factor Xa and synthetic substrate are set out. This type of assay is a convenient way to measure enzymatic activity. The assay described in the Application is a chromogenic assay which, as I described above at paragraph 68, was a standard in vitro assay and the biochemist would have been very familiar with it at the priority date. The S2222 substrate is a classic factor Xa substrate for use in this assay.*

84. *The assay described in the Application uses a short peptide (a modified tetrapeptide) with a dye coupled to it through an amide bond. The coupling changes the absorption characteristics of the dye. When the short peptide docks into the active site of the enzyme, the amide bond is broken and the dye is released. The free dye then absorbs visible light, resulting in an intense yellow color which allows the biochemist to follow the enzyme reaction in real-time. If an inhibitor docks into the active site instead, then the short peptide cannot access the active site and the dye remains coupled to it and does not turn yellow. A lack of color therefore indicates enzyme inhibition. The results of the assay can be expressed as an inhibitory constant, K_i. The lower the K_i value, the better the inhibition.*

85. *Page 170 of the Application ([0116] of the Patent) explains that compounds tested in the assay were considered to be active if they had a K_i value of $\leq 10\mu M$, with the most preferred compounds having a K_i of $\leq 0.001\mu M$. The biochemist would agree that a K_i of $\leq 0.001\mu M$ indicates that the inhibitor in question is very potent. No data are provided in the Application or the Patent for any specific compounds that were tested.*

86. *Page 170 of the Application ([0117] on page 84 of the Patent) then goes on to discuss an in vivo test in rabbits which can be carried out to determine the potential antithrombotic effect of compounds. The Application describes a rabbit arterio-venous (AV) shunt model and how these AV shunt models would be carried out. It explains that the test allows the biochemist to estimate an ID_{50} value (dose which produces 50% inhibition of thrombus formation). As explained in paragraph 73 above, this tells the biochemist whether or not the compound being tested has anti-clotting properties.*

87. *In general, the more potent the inhibitor, the more likely it is that the ID_{50} will be lower. No data are provided in the Application or the Patent for any specific compounds that were tested using this in vivo model.*

88. *It has been shown to me that 3.07g of the compound in Example 18 was synthesised. This would be more than enough compound to run standard animal studies, including an AV shunt model.*

89. *In 2007, Donald Pinto (one of the named inventors of the Patent), published a paper providing data for apixaban (also referred to as compound 40/BMS-562247 in the paper). This is Appendix JHM8 to this witness statement. Supporting information referenced in JHM8 was also published by the journal online and that is included as Appendix JHM9.*

90. *If the skilled team had carried out the standard in vitro chromogenic assays and the rabbit AV shunt model referred to in the Application in September 2001, they would have been expected to get the following results for apixaban:*

Test	**Result (nM)**	**Reference in JHM8**
In vitro chromogenic assay (to assess potency to inhibit factor Xa) using human factor Xa	0.08 K_i	Table 6, page 5346
In vitro chromogenic assay (to assess potency to inhibit thrombin) using human thrombin	3100 K_i	Table 5, page 5346
Rabbit AV shunt model	329 IC_{50}	Table 6, page 5346

91. *Additional data on apixaban is provided in Table 6, page 5346 of JHM9, and in Table 8 of*

JHM9. Pinto concludes, on page 5347 of JHM8, that apixaban "is a potent, selective, and orally bioavailable fXa inhibitor".

Validity of the Patent

Plausibility

92. I have identified the person skilled in the art and the common general knowledge above.

93. I have been asked to consider the question of plausibility. As part of my instructions in this case, I have been told that the legal standard in relation to a claim to compounds for a therapeutic use requires that the use of the claimed compounds for the claimed therapy would have been plausible to the skilled team. I have been instructed that the issue is whether the Application discloses some reason for supposing that the assertion of efficacy is true. There must be reasonable scientific grounds for the skilled person to expect that the compounds might well work to treat the claimed indications. I have been told that this does not necessarily require that the patent shows the claimed compounds working in humans for that therapeutic indication. I have been instructed that animal tests or, in some cases, in vitro tests may be sufficient to make it plausible that claimed compounds will be effective for a claimed therapeutic use and that a theory for how the claimed invention is said to work can be taken into account. I have been instructed that in each case the skilled person is assessing plausibility in light of the disclosure of the Application and the CGK.

94. I have been asked to consider the question, whether, if a compound had been identified as being an effective factor Xa inhibitor in September 2001, the biochemist would anticipate that the compound would be a good candidate for a drug to treat thromboembolic disorders. For the reasons that I discuss in the CGK section above and summarise below, the biochemist would anticipate that the compound would be a good candidate for a drug to treat thromboembolic disorders:

a. due to factor Xa's position and role within the coagulation cascade, the biochemist would have anticipated that inhibiting factor Xa would slow down or prevent clot formation (see paragraph 64.A above);

b. several synthetic direct factor Xa inhibitors had already shown promising results in animal models and had moved on to clinical trials (see paragraph 67 above); and

c. LMWH (predominantly an indirect factor Xa inhibitor) was already being used successfully in the clinic and fondaparinux, an indirect factor Xa inhibitor, was showing very encouraging results in phase II and phase III trials confirming the hypothesis that compounds which targeted factor Xa were good candidates for a drug to treat thromboembolic disorders (see paragraphs 55 to 59 above).

[*Footnotes*]

[1] Citrated plasma is a very common substrate for almost all coagulation-specific laboratory tests. It is derived from whole blood drawn into a tube which contains liquid 3.2% sodium citrate (109 mM). The citrate acts as a calcium chelating agent to prevent coagulation of the sample so that all the clotting factors are preserved and can be evaluated.

[2] Stephanie A. Smith, Richard J. Travers & James H. Morrissey (2015) How it all starts: Initiation of the clotting cascade, Critical Reviews in Biochemistry and Molecular Biology, 50:4, 326-336, DOI: 10.3109/10409238.2015.1050550.

[3] Appendix JHM2 says 2001 at the top of the first page but the textbook was published in December 2000.

[4] Note that currently accepted nomenclature guidelines are to drop the 'III' and refer to this protein as simply 'antithrombin' or 'AT' rather than AT-III.

[5] The dissociation constant describing the binding affinity between the inhibitor and the enzyme.

[6] Nanomolar potency is the level of potency that the skilled team would generally be looking for when testing potential inhibitors."

Statement #2 of 2

"*Reply to the Gallagher Statement*

1. *I have been provided with a copy of the Gallagher Statement and have been asked to review and comment on it.*
2. *Figure 1 provided at paragraph 6.15 is significantly out of date – it omits that the tissue factor/factor VIIa complex also activates factor IX to IXa, something that was known since the late 1970s. I do not recognise the book this figure is taken from. This is a minor point and I do not believe it has any relevance to the subject matter at issue here.*
3. *Dr Gallagher refers to the skilled pharmacologist whereas I refer to the skilled biochemist, though I do not believe anything turns on that.*
4. *At paragraph 6.22.2(b), Dr Gallagher describes 'The antithrombotic effect of an inhibitor has to be balanced against its effects on hemostasis (normal clotting) so the lower the dose, the lower the likelihood of serious bleeding side effects' as a widely accepted general principle related to potency. I find this a bit confusing. The relevant point about dosing is that you need to dose an inhibitor relative to its ability to inhibit factor Xa so as to partially inhibit factor Xa to the required degree.*
5. *At paragraph 6.22.3 of the Gallagher Statement, Dr Gallagher says: 'The Ki is the concentration of inhibitor required to produce half maximal inhibition.' That is the definition of IC_{50}, not K_i. K_i is the affinity of the inhibitor for the target enzyme and is a constant whereas the IC_{50} will vary depending on the substrate concentration. Dr Gallagher's description of what is IC_{50} is also, by my reading, not fully accurate – IC_{50} is generally and would at the priority date have been understood as being referable to the concentration at which 50% of the activity is observed, as opposed to Dr Gallagher's definition, which is by reference to the concentration at which 50% of the maximum effect of the inhibitor is observed.*
6. *At paragraph 6.23, Dr Gallagher comments on the selectivity of compounds for factor Xa inhibition. He says: 'In the FXa inhibitor field in 2001, a compound would be considered selective if it has at least three orders of magnitude or more lower potency against these enzymes than against FXa.' Three orders of magnitude of difference would be ideal but I disagree that it would be necessary for a compound to have that level of selectivity for a drug development team to progress with it.*
7. *At paragraph 6.24.2, Dr Gallagher lists a number of clotting tests that could be used, including a thrombin time clotting test that I do not believe would be sensitive to factor Xa inhibitors.*
8. *At paragraph 8.3, Dr Gallagher says: 'Determining if the goal of useful FXa inhibition is likely with the compounds under this invention would require substantial work to establish whether or not the properties of the compounds meet the expectations described above'. In so far as Dr Gallagher is talking about running basic screening tests of the relevant compounds I would not describe that as substantial work. Running assays to measure IC_{50} and selectivity would be routine and many thousands of such assays can be run over the course of a few days. Dr Gallagher also refers here to chemical structures that 'could be tested' whereas the patent describes that some of the compounds have been found to exhibit a K_i of less than or equal to 10 μM.*
9. *At paragraph 8.7.4, Dr Gallagher refers to the 'impressively complete list of potential clinical conditions for FXa inhibitors' and goes on to say: "No guidance, however, is provided to help determine which of these potential clinical indications would be most likely to benefit from FXa inhibitors." I do not think it reasonable to expect guidance of that nature in a patent application, particularly one describing chemical compounds that had not been subject to clinical trials.*
10. *At paragraph 8.7.15, Dr Gallagher discusses a sentence from the Application addressing utility for diseases arising from elevated thrombin activity. I do not read that sentence as necessarily referring to the use of the compounds as thrombin inhibitors, as such, but could refer to their use as factor Xa inhibitors which would have the upstream effect of reducing thrombin generation.*

11. *At paragraph 8.7.16, Dr Gallagher describes testing for selectivity. The necessary proteases and their chromogenic substrates were readily available and the tests would have been done as a matter of routine for a drug development team.*"

APPENDIX 10

Abridged Written Evidence of Dr Rasser

"***[1.]*** *Company Policy in relation to intellectual property rights ("IPR") ownership*

…

5.4. *…*[A]*t P&G, it was commonly understood that we needed to make sure that at all times assignments were in place to ensure that the entire ownership of IPRs was indeed in the hands of the correct corporate entity. We accepted that this carried an administrative burden and costs but it was widely seen as an important part of good corporate housekeeping.*

5.5 *The structure required an occasional internal transfer of rights to deal with a specific situation. By way of example, for purposes of infringement litigation proceedings outside the US, a national patent would be assigned to the local subsidiary in that country so that the plaintiff initiating the proceedings would be the entity that suffered the damages in that respective country.*

5.6 I was a member of the Association of Corporate Patent Counsel ('ACPC') which organized conferences twice a year. The Chief Patent Counsel of many large US companies were members. At these conferences there were presentations about how various companies organized their IP function. The ACPC also conducted benchmarking studies on these topics. Making sure that IPRs were held by the right entity was important not just for what I call the 'IP kitchen' of a company, i.e. IP specific issues like priority claims, but importantly also for the tax department and for compliance reasons in general.

[2.] My views as to the witness statement of Paul Golian and the Policy at BMS after the acquisition of Dupont

…

6.6 [BMS's decision]*, which was implemented, was to keep existing IP in BMS Pharma Company, and to assign any new IP to BMS Company. Because BMS Pharma Company was just the new name of the recently acquired DuPont business, all that was required was a name change. This, apparently, was an important consideration:* 'Effecting name changes was less costly and time consuming than it would have been to have Bristol-Myers Squibb Pharma Company assign all those rights to BMS Co.' (paragraph 12).

6.7 *Although I understand this desire to minimize the administrative burden and cost, it resulted in a split of the IP: the legacy DuPont IP with legal title was to be held by BMS Pharma Company; and all new IP (see paragraph 8, last line of quote), with legal title held by BMS Company. This split would have set off alarm bells in my mind. The set-up was no doubt clear and straightforward to those who developed and implemented it. But it would have to be administered by others in future years who were not privy to the decision. In my experience such complexities are invitations for errors. Ultimately BMS Company simply chose, at the time, not to transfer legal title to BMS Company and as such created this split of IP which left the door open for risk.*

6.8 *In any event, as noted, the Inventors assigned their rights on November 3, 2001, to BMS Pharma Company which was after the recommendation by Ms. Yonco-Haines of October 24, 2001. The inventors could have been asked to assign their rights to BMS Company, instead of to BMS Pharma Company. This would not have incurred any additional administrative burden or cost. That this was not done suggests to me that there was another, perhaps tax-related, reason to leave legal title of the legacy IP with BMS Pharma Company.*

6.9 *In any event, even if the decision whether to place legal title with BMS Company or BMS Pharma Company was without any consequence, once the decision was made it was important to stick with it and not to take any actions that were inconsistent with it. If, for*

example, during the Priority Year, BMS acknowledged that the patent application should have been assigned to BMS Company, it could have easily corrected the situation with an assignment from BMS Pharma Company to BMS Company. Or, in the alternative, it could have filed the PCT Application in name of BMS Pharma Company. The one thing it could not do is keep the priority filing in name of BMS Pharma Company and submit the PCT filing in name of BMS Company. Yet, this is exactly what it did.

6.10 *As follows from the above, BMS's handling of the IP allocations is in stark contrast with my personal experience and what was common at the time (around 2001). IPR ownership (including having the legal title) was considered very carefully and executed with precision and consistency including the assignment of IPRs to the entities where these rights belonged. This holds especially true for heavily regulated companies like P&G and BMS. It was well understood that it was necessary and important for more than just the operation of IP, but as I explained above, also for transfer pricing and national taxation in different subsidiaries.*

[3.] *My specific views as to the assignment of priority rights*

7.1 As mentioned above, I have been informed that the issue of priority rights arises in these proceedings. I note, however, that Paul Golian does not specifically address priority rights. The statement refers generally to 'patents and patent applications'.

7.2 In the context of priority, I can say that we all knew at P&G, and I can think of no reason why this would be different at BMS, that priority rights can be subject to different rules across the world. So, with respect to priority rights we knew that we had to make sure that we were compliant with the different requirements, including both substantive and formal requirements, as to who owned such rights from different jurisdictions in which our patent families were granted, including European patents.

7.3 We were well aware that when it comes to assignments, in general, but also specifically for priority rights, that these had to be executed by way of a written document that would be signed by the assignor and the assignee. To the best of my knowledge this was accepted as proof of assignment, including in Europe. Failure to do so could result in an invalid claim to priority and the patent could risk being held invalid as a result. This was a critical concept for companies whose business was centred on generation and exploitation of IP. For example, researchers would know that they could not publish their work until the relevant priority application had been filed."

APPENDIX 11

Abridged Written Evidence of Mr Rennie-Smith

Statement #1 of 2

"***Succession in title of priority rights***

14. *The right to priority is governed by Article 4 (A)1 of the Paris Convention and Article 87 of the EPC. Article 4 (A)1 of the Paris Convention provides:*

"Any person who has duly filed an application for a patent, or for the registration of a utility model, or of an industrial design, or of a trademark, in one of the countries of the Union, or his successor in title, shall enjoy, for the purpose of filing in the other countries, a right of priority during the period hereinafter fixed." [underlining added]

Article 87(1) EPC provides:

"A person who has duly filed in or for (a) any State party to the Paris Convention for the Protection of Industrial Property, or (b) any Member of the WTO, an application for a patent or the registration of a utility model or for a utility certificate or for an inventor's certificate, or his successor in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application." [underlining added]

15. *Thus Article 87 EPC provides that the person who has filed the priority application or his successor in title is entitled to claim priority. The use of the singular form 'successor in title' rather than the plural form 'successors in title' has no significance. If the earlier priority application has been filed by two or more persons, then both or all those persons or their successor or successors in title must be applicants for the later European application. Further, the later application can be applied for by one or more additional applicants provided the earlier applicant or applicants are applicants also. If a succession in title to the priority right is relied on, the transfer of the right must have taken place before the filing date of the later European application. (See 'Guidelines for Examination in the European Patent Office', March 2022 edition, Part A, Chapter III, section 6.1, page III-8.)*

16. *Neither the Paris Convention nor the EPC provides any regulations or requirements to establish that a succession in title is valid. In particular, the EPC does not contain any provisions which must be fulfilled in order for an assignment of priority rights for the filing of a European patent application to be considered valid for Article 87 EPC. This absence of any provisions in the EPC means that the EPO conducts the assessment of succession in title to priority right on the basis of national law. Which is the appropriate national law to be applied and whether the requirements of the appropriate law have been fulfilled are both questions which are considered on the facts of each case (and might even require separate consideration for each of two or more joint applicants for the priority application). The guidance provided by the case law of the Boards of Appeal is largely confined to confirming that the validity of succession is a matter of national law and otherwise must be decided on a case-by case basis on the facts of each case under the applicable national law (see 'Case Law of the Boards of Appeal of the European Patent Office', 9th edition 2019 (the "Case Law Book"), pages 401-404). The decision in case T 1201/14 of 9 February 2017 also provides, in addition to analysis of the facts of that case, helpful summaries in section 3 (pages 19 to 45) of the case law which preceded it.*

17. *As I have indicated above, the determination of the applicable national law is not a matter which is dictated by case law but a matter which depends on the facts. In some cases, the*

Boards of Appeal have simply determined that the law of the state of the priority application (or claimed priority application) is the applicable national law. This was the case in, for example, J 19/87 of 21 March 1988 (English law), T 1008/96 of 25 June 2003 (Italian law), T 493/06 of 18 September 2007 (English law) and T160/13 of 23 April 2015 (German law). As was suggested in T 205/14 of 18 June 2015 (see paragraph 3.6.3 of the reasons), in those cases

'...the determination of the applicable national law seems to have been straightforward in view of the circumstances of the respective cases.'

18. *In other cases, the Boards of Appeal have considered the possibility of the application of each of two or more national laws. Thus, in T 205/14 (and the related case T 517/14 of 19 June 2015) the Board considered both the law of the priority application (US law) and the law of the contractual relationship between the transferring parties (Israeli law) and, on the facts, decided the latter was the applicable national law. In T 1201/14, the Board considered no fewer than four lines of argument concerning US, German and Taiwanese law before deciding that, irrespective of which national law might be applicable, no succession in title could be established.*

19. *The relevant provisions of the applicable national law are supplied in the form of evidence such as the text of national legal provisions or, ideally, the written opinion of a lawyer from the jurisdiction in question with appropriate expertise (see T 1103/15 of 22 February 2018, paragraph 1.5 of the reasons - a case concerning priority entitlement; and T 74/00 of 15 March 2005, paragraph 4 of the reasons - a case concerning transfer of an opposition, another issue which requires the EPO to refer to national law). Such an opinion will typically both set out (or attach) the relevant provisions and explain their significance for the facts of the case. Thus, in J 19/87 evidence of English law was provided by the written opinion of an English patent barrister and in T 205/14 evidence of Israeli law was provided by two written opinions of an Israeli patent lawyer.*

20. *In the present case (if the issue of succession in title were to be decided in the EPO) the facts indicate very strongly that the applicable national law would be the law of the state of Delaware in the USA. The USA is the state (in the sense of the country) of the priority application and, as is well-known, in the USA patent applications are governed by federal law. However, the law of incorporation of all the corporate entities in question and thus the law governing the relations between those entities and the ownership of their assets, including the right to claim priority from the US priority application, was that of the state (in the sense of a member state of the USA) of Delaware. Indeed, there does not appear to be an alternative so the choice of Delaware law as the appropriate national law appears 'straightforward' in the sense suggested in T 205/14 (see paragraph 17 above).*

21. *Strictly speaking, there are in the present case two steps in the succession in title to the right to claim priority from the application US 324165. Since the applicants named on that application were the inventors Pinto and Quan, the first step was their assignment of 3 November 2001 of their rights in US 324165 (including the right to claim priority from it) to BMS Pharma. This assignment identifies the application by its case number, application number and date, and specifically includes as one of the items of assigned property 'any priority rights derived from the aforesaid application'. Whether viewed as a matter of Delaware law (because the inventors were employed by and were contracting with a Delaware corporate entity) or as a matter of US federal law (because the assignment arose from a US patent application), the words of the document are so clear as to be unambiguous. I have no doubt that, if required to consider the document, the EPO would find that it had the effect as of 3 November 2001 of making BMS Pharma the successor in title to the priority right of the two inventors.*

22. *The second step was then a further succession in title to the priority right by BMS Co from BMS Pharma by virtue of the legal relationship between BMS Co and its wholly owned subsidiary which gave rise to an equitable title by BMS Co to the priority right. For the reasons I mentioned in paragraph 20 above, that would have to be established as a matter of Delaware law. I note from his Statement that Chancellor Chandler answers the two*

questions he was asked with emphatically affirmative opinions, agreeing with the conclusions set out in an expert report of Randy J. Holland, former Justice of the Delaware Supreme Court, dated June 29, 2021, when considered in light of the matters set out in the Golian Statement. First, it is his opinion that as a matter of Delaware law at the date of filing of the PCT application BMS Co had the unfettered right to call for the assignment to it by Bristol-Myers Squibb Pharma Company of the right to claim priority from US 324165. Second, it is his opinion that as a matter of Delaware law at the date of filing of the PCT application BMS Co could be characterized as the beneficial owner of US 324165.

23. *Chancellor Chandler's reasons for reaching those opinions appear from paragraphs 15 to 17 of the Chandler Statement, where he agrees with and adopts Justice Holland's statement of Delaware law and applies the analysis set out in the Holland Expert Report to the facts presented in the Golian Statement. At the date of filing of the PCT application BMS Co, being the entire owner of its subsidiary BMS Pharma, was the beneficial owner of its subsidiary's assets including the right to claim priority from US 324165. The bare legal title to that right was owned by the subsidiary but BMS Co as beneficial owner had complete control over the exercise of the right and could demand the assignment to it of the right. The distinction between beneficial title - also often referred to as equitable title - and legal title is familiar to lawyers from common law legal systems (such as those of Ireland, England and most states of the USA) and equitable title has been accepted by the EPO as a principle of national law underlying a succession in title to a right to claim priority.*

24. *I see no reason why the EPO would not accept Chancellor Chandler's expert evidence of Delaware law as demonstrating that BMS Co was the successor in title to the right to claim priority. As I have explained, in the EPO succession in title to the right to claim priority is decided according to the appropriate national law and thus the first step is to decide which national law to apply. Then if, in the second step of applying that law to the case in question, that national law is one, such as Delaware law or English law, which allows succession in title by the transfer of an equitable title then, assuming the EPO is satisfied that this has taken place, it will acknowledge a valid succession in title.*

25. *To the best of my knowledge the earliest case in which an equitable title was found to demonstrate succession in title to a priority right under Article 87(1) EPC was J 19/87 (a decision of 21 March 1988). In that case the applicant for a European patent had previously been advised that the assignment to him of the invention and the UK priority patent application had no legal effect because he had not signed it. However, according to the reasoned expert opinion of an English patent barrister, which the Board accepted as correctly representing the relevant English law, the assignment did have the legal effect that the applicant became the owner of the invention and entitled in equity (that is, he had an equitable title) to the UK application. He was entitled to apply for and be granted a European patent in respect of the invention the subject of the UK application and also, for the purpose of filing the European patent application, a right of priority.*

26. *This has more recently been confirmed in decision T 577/11 of 14 April 2016 (pages 73- 76). In T 577/11 Technical Board of Appeal 3.2.05 summarized the facts and the findings of J 19/87 with apparent approval of that decision on the facts of that case. However, the Board declined to accept, as was argued by the appellant, that succession in title on a quite different basis - economic ownership in Dutch law - was the same as ownership in equity. In a yet more recent case (T 1786/15 of 15 October 2020, see paragraph 16 of the reasons) the patent proprietor raised an argument based on transfer of equitable title but did not pursue it when the Board indicated the evidence was insufficient, so it was not decided whether such a transfer would have been valid.*

27. *In my opinion, on the facts of the present case including the expert opinion of Chancellor Chandler (a lawyer from the jurisdiction in question with appropriate expertise - see paragraph 19 above) the EPO would, if required to decide the issue of priority entitlement, apply Delaware law as the appropriate national law and, in accordance with that law as set out and applied by Chancellor Chandler, accept that at the date of the PCT application BMS Co had an equitable title to claim priority from US 324165. In short, the EPO would find sufficient basis for a valid succession in title under Article 87 EPC.*

28. *I am not aware of any EPO case law which decided that the transfer of an equitable title*

would not be sufficient basis for a valid succession in title.

29. *For completeness, I mention here that questions relating to entitlement to priority have recently – since I made the statement referred to in paragraph 8 above – been referred to the Enlarged Board of Appeal. Strictly speaking, there are two referrals of the same questions in two related cases now pending as G 1/22 and G 2/22. One of the questions is whether the EPO has jurisdiction to determine the validity of claims to succession in title under Article 87(1) EPC. In my opinion the referral of that question is inadmissible but, if admissible, likely to be answered in the affirmative. Further, whether or not admissible and, if admissible, whether the answer to the question is affirmative or negative, national courts in Europe will still be required to decide such issues and in doing so will take account of the existing case law of the boards of appeal*."

Statement #2 of 2

"*4. In my first witness statement, I expressed the opinion that under the law and practice of the EPO the claim in European Patent EP1427415, of which BMS Ireland is the proprietor, to priority from the United States provisional patent application US 324165 would be considered valid. I maintain that opinion notwithstanding the views expressed by Dr Kinkeldey.*

5. I shall use the same abbreviations in this statement as set out in my first witness statement.

6. In the section titled 'Comments' of this statement I shall comment on particular paragraphs of Dr Kinkeldey's opinion and then in the section titled 'Observations' I shall make some overall observations.

Comments

7. *In paragraph 25 of her opinion, Dr Kinkeldey says that* 'Article 87 (1) requires that it has to be sufficiently clear that there was an agreement and what was agreed'. *In fact, Article 87(1) EPC – which I quoted in full in paragraph 14 of my earlier statement – makes no mention of an agreement and has no words which could possibly suggest a requirement for an agreement.*

8. Dr Kinkeldey mentions in her paragraphs 26 to 30 the very recent referrals to the Enlarged Board of Appeal ('EBA') now pending as G 1/22 and G 2/22, which I commented on in my first witness statement, and I agree with her that the referrals relate principally to the so-called 'joint applicants approach' to claims to priority. I would add that that approach, the validity of which is now subject to the EBA's decision, does not require an agreement or assignment.

9. In paragraphs 31 to 33 of her opinion, Dr Kinkeldey refers to the witness statement of Paul Golian ('Mr Golian's Statement'*) and concludes that this provides no evidence of a transfer of the right to claim priority. I disagree with that conclusion and would also add that the evidence of such a transfer is not just Mr Golian's Statement but also the witness statement of, and evidence to be given by, Chancellor Chandler.*

10. Dr Kinkeldey also says in paragraph 33 of her opinion that '...Article 87 (1) EPC, at a minimum, requires that there has been an assignment of the particular priority right in question and that this is proven'. *I question whether that is correct. The EPC no more requires an* 'assignment' *than it requires an* 'agreement' *(I refer to paragraph 7 above).*

11. In paragraphs 34 to 39 of her opinion Dr Kinkeldey says she is 'not aware of any EPO case law stating or confirming that having 'equitable title' is sufficient to qualify as a successor in title'. However, she then refers to J 19/87 in which that was exactly the outcome. She then concludes that 'J 19/87 does not take away the basic requirements for succession in title under Article 87 (1) EPC'. *She appears to see equitable title as an alternative to succession in title whereas in fact the case law shows that equitable title is just one way of establishing succession in title.*

12. In her paragraph 38 Dr Kinkeldey lists four comments which she says 'the Boards' (in the plural) have made of J 19/87. I note that in fact those comments are from just one paragraph of one decision by one board, namely T 577/11 of Technical Board of Appeal 3.2.05. As I

mentioned in my previous statement (paragraph 26), that decision approved of J 19/87 as being correct on its facts. In other words, it confirmed that an equitable title could give rise to a succession in title under Article 87(1) EPC.

13. *In paragraph 40 of her opinion, Dr Kinkeldey provides her conclusion that she* '[has] seen no evidence at all that there has been a transfer of the right to claim priority from US'165 from BMS Pharma to the later PCT-Applicant, BMS Company'. *I do not find it surprising that Dr Kinkeldey sees no evidence of a transfer – if, as she asserts, a transfer or succession in title requires an agreement or an assignment, then she would not recognise any other form of succession such as by equitable title.*

Observations

14. *In so far as it is the Petitioner's case that transfer of the right to claim priority from a priority application can only be established by a conclusive agreement, anything else would not be sufficient. But there is in fact no such requirement at all in Article 87 EPC or in the Guidelines or in the case law of the Boards of Appeal. It is of course easy to establish a succession in title if there is an agreement which proves a transfer but that is not a sufficient reason to maintain that such an agreement is a necessary requirement.*

15. *As I explained in paragraphs 14-28 of my first witness statement, the EPC and the Paris Convention only require a succession in title but have no requirements how that succession should be established. Thus, as the case law shows, the EPC considers on a case by case basis which national law should apply and whether the requirements of that law have been fulfilled. One manner of establishing succession in title in several cases has been by proof of equitable title under the national laws of countries (such as England and the USA) whose laws include the doctrine of equitable rights.*

16. *Equitable title can arise in many situations including a less than fully executed agreement (as for example in J 19/87), an employment contract (as for example in the opposition to EP2215124) or indeed, as explained by Chancellor Chandler, in the circumstances of the present case.*

17. *Dr Kinkeldey says, apparently by way of criticism, that J 19/87 is a very old case and the only case which dealt with equitable title. I find the first criticism strange – long established and unchallenged case law is usually considered more authoritative. Moreover, as I have already noted, J 19/87 has been approved in the more recent decision T 577/11 (which was issued some 28 years later).*

18. *Nor is J 19/87 the only case dealing with equitable title to come before the EPO. In my experience, equitable title arising from employment of inventors has arisen many times. I mentioned above the opposition to EP2215124 as this is a case of which I happen to have personal knowledge. In that case, equitable title was relied on and, as appears from the preliminary opinion of the Opposition Division, accepted by it as established (although in its ultimate decision it found succession in title by the 'joint applicants approach').*

19. *I also refer to the decision T 844/18 of 16 January 2020 (also mentioned by Dr Kinkeldey in paragraph 27 of her opinion in the context of the recent referrals to the EBA). In points 63 to 65 of that decision, board 3.3.08 refers to equitable title – which did not apply in the case before it – in the context of an English national law decision and observed:*

> *'The case turns upon the distinction in English law (and US law) between legal and equitable ownership. According to English law it is the equitable owner who should be the applicant for the subsequent international patent application and not the bare legal owner.'*

Thus, that board in a recent decision had no difficulty with the concept of equitable title."

APPENDIX 12

Abridged Written Evidence of Mr Steele

"*I have reviewed the Holland Report and have been asked to provide my observations and comments on two general topics addressed in that report.*[20] *While that Report is not part of the Irish Proceedings, I understand that it may be of assistance for me to address these two topics that BMS Ireland and its expert witnesses have advanced in other related proceedings in other jurisdictions….*

22. *In general terms, my views are as follows: (i) I agree that BMS Ireland and its wholly owned subsidiary BMS Pharma Company are distinct legal entities under Delaware law, and (ii) I disagree that under Delaware law BMS Company had 'unfettered' and 'absolute' rights with respect to the patents owned by its subsidiary BMS Pharma Company. Also, while I am not an expert in patent law, I understand that U.S. federal law governs the acquisition and ownership of patents. See* Digitech Image Techs., LLC *v.* Newegg Inc.*, 2013 WL 1871513 (C.D. Cal. May 3, 2013) (*'Patent rights are not acquired unless authorized by, and acquired in, the manner prescribed by statute*'). For that understanding, I rely on the Digitech decision and my general understanding of how patent law works based on my being a member of the Delaware judiciary for 25 years, but otherwise defer to the Expert Statement of Professor John R. Thomas. The Holland Report did not address U.S. federal law governing the acquisition and ownership of patents.*

Topic 1: BMS Company and BMS Pharma Company are separate legal entities under Delaware law.

23. *In paragraph 22 of the Holland Report, … Justice Holland wrote, '*As a general principle of Delaware law, a corporation is viewed as a separate legal entity, independent from its stockholders, directors, and officers as well as its parent, subsidiaries, and affiliates.*' I agree with that statement. Indeed, 'Delaware embraces and will protect 'corporate separateness."* Manichaean Capital, LLC *v.* Exela Technologies, Inc., *251 A.3d 694, 713 (Del. Ch. 2021) (citing* NAMA Holdings, LLC *v.* Related WMC LLC*, 2014 WL 6436647, at *26 (Del. Ch.) and* Pauley Petroleum, Inc. *v.* Continental Oil Company, *231 A.2d 450, 454 (Del. Ch. 1967) (*'[T]he law must and does respect the separateness of the corporate entity ….'*)); see also* Paul Elton, LLC *v.* Rommel Delaware, LLC*, 2020 WL 2203708, at *14 (Del. Ch.) (*'Delaware public policy disfavors disregarding the separate legal existence of business entities.'*);* Wallace *v.* Wood*, 752 A.2d 1175, 1183 (Del. Ch. 1999) (*'Persuading a Delaware court to disregard the corporate entity is a difficult task.'*) (citations omitted).*[21]

24. *The Holland Report cited* Hollinger, Inc. *v.* Hollinger International, Inc.[4] *for the principle, raised in dicta in the Hollinger decision, that corporate separateness does not apply in all contexts…The Holland Report then described two contexts in which corporate separateness does not apply: (i) a stockholder request for a corporation's books and records pursuant to Section 220 of the Delaware General Corporation Law ('DGCL') and (ii) the application of Section 271 of the DGCL to the sale of all or substantially all of a corporation's assets….*

25. *Both contexts are limited to the statutory provisions to which they relate.*

26. *Section 220 of the DGCL governs a stockholder's right to demand that a Delaware corporation produce books and records to the stockholder. In 2003, Section 220 of the DGCL was amended to allow a stockholder of a parent corporation to demand that the parent corporation produce its wholly owned subsidiary's books and records if the stockholder meets the requirements of Section 220. While this amendment blurs the line of*

[20] To the extent aspects of the Holland Report were adopted and referred to in the Rennie-Smith Report, my observations, comments and conclusions equally apply to the Rennie- Smith Report.

[21] *The United States Supreme Court likewise recognizes corporate separateness as a* 'basic tenet of American Corporate law.' Dole Foods Co. *v.* Patrickson*, 538 U.S. 468, 474-75 (2003) (*'A basic tenet of American corporate law is that the corporation and its shareholders are distinct entities.'*).*

corporate separateness between a corporation and its wholly owned subsidiary, the synopsis to the 2003 amendment states that 'it was '**not intended to affect** existing legal doctrine that, as a general matter, **respects the corporate existence of subsidiaries** in relation to liability of stockholder to third parties, personal jurisdiction over subsidiaries of Delaware corporations, and discovery in litigation other than under Section 220.'.... *(emphasis added) In other words, the 2003 amendment to Section 220 affects the legal doctrine that respects corporate separateness only in the context of a Section 220 demand for books and records. Section 220 of the DGCL does not refer to and has no relevance to the assignment or ownership of patents.*

27. *Section 271 of the DGCL governs the sale of all or substantially all of a Delaware corporation's assets and establishes the authorization required from the corporation's board of directors and stockholders to effect the sale.* 'For purposes of [Section 271] **only**, the property and assets of the corporation include the property and assets of any subsidiary of the corporation.' *8 Del. C. § 271(a) (emphasis added). Thus, the assets of the subsidiary are treated as assets of the parent for purposes of applying the requirements of Section 271(a), and not for any other purpose.*[8] *Section 271 does not refer to and has no relevance to the assignment of patents. Section 271 does not refer to patents and has no direct relevance to the ownership of patents outside the context of a sale, lease, or exchange of assets under Section 271.*

28. *A third context in which corporate separateness may not apply is veil piercing, in which a court disregards an entity's legal form. The Holland Report did not address veil piercing. Delaware courts consider various factors in determining whether to disregard the legal form, including:* '(1) whether the company was adequately capitalized for the undertaking; (2) whether the company was solvent; (3) whether corporate formalities were observed; (4) whether the dominant shareholder siphoned company funds; and (5) whether, in general, the company simply functioned as a facade for the dominant shareholder.' Doberstein *v.* G-P Industries*, 2015 WL 6606484, at *4 (Del. Ch.). I am not aware of any facts that would suggest that the foregoing factors would apply to BMS Pharma Company or that its separate legal existence should be disregarded.*

29. *It is my opinion that these two contexts where corporate separateness may not apply - a books and records demand under Section 220 of the DGCL and a sale of all or substantially all of a corporation's assets under Section 271 of the DGCL -- are not relevant to the question of whether BMS Company and its wholly owned subsidiary BMS Pharma Company are distinct legal entities for the purposes of the patent dispute. It is also my opinion that, based on the facts known to me, there is no reason to disregard the separate legal existence of BMS Pharma Company and BMS Company under Delaware law. In conclusion, it is my opinion that BMS Company and BMS Pharma Company are distinct legal entities under Delaware law.*

Topic 2: BMS Company does not as a matter of Delaware law have 'unfettered' or 'absolute' rights in its wholly owned subsidiary BMS Pharma Company.

30. *I disagree with the following two opinions that Justice Holland offered in his report: First, he opined that* 'as a matter of Delaware law, when BMS filed the later patent application in 2002, by virtue of its 100% ownership of its subsidiary Bristol-Myers Squibb Pharma Company, and its stated internal policy as to patent filings, BMS had the <u>unfettered</u> right to call for such subsidiary to assign to BMS the right to claim priority from the earlier filed patent application.'[22] *Second, he opined that* 'BMS had and has the <u>absolute</u> right to direct the legal title holder of the patent, Bristol-Myers Squibb Pharma Company, to take any and all action regarding the patent that is in the best interest of BMS.'[23]

31. *As previously held in* Digitech Image Techs., LLC *v.* Newegg Inc.*,*

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[22] *Id. at 34 (emphasis added).*

[23] *Id. at 39. Justice Holland also opines that* 'BMS could be treated as successor in title to such subsidiary under the Paris Convention, as I understand that term has been interpreted by the English courts, according to the cases cited in the legal background provided to me' *Id. At 34. I am not an expert on the term 'successor in title' as used under the Paris Convention or as interpreted by the English Courts and therefore do not offer an opinion on whether BMS could be treated as a successor in title under the Paris Convention….*

> 'The fact that a corporate parent's subsidiary owns a patent is not enough to establish that the parent has a legal ownership interest in the subsidiary's patent. Abraxis Bioscience, Inc. v. Navinta LLC, 625 F.3d 1359, 1366 (Fed.Cir.2010) (finding that common corporate structure does not overcome the requirement that, **even between a parent and a subsidiary**, [emphasis added] a written assignment is necessary for the parent to have legal title to the patent).

It then follows that a parent-subsidiary relationship is likewise insufficient to establish equitable title to a patent. This conclusion is in harmony with Federal Circuit law. The Federal Circuit has never held that a corporate parent has equitable title in a subsidiary's patents. In addition, several district courts have held that the mere fact that a corporation's subsidiary owns a patent is insufficient to establish that the corporation has equitable title to the patent.'
*2013 WL 1871513, at *4 (C.D. Cal. May 3, 2013).*

32. *Further, the mere possibility for a corporate parent to instruct a subsidiary to assign an asset does not, under the laws of Delaware, equate to an assignment actually carried out. In this regard, I agree with the Thomas Report, in which Professor Thomas states that Delaware law would* 'govern the interpretation of particular contractual elements of an assignment,' *but federal law would govern the transfer of patent rights… As federal law governs the transfer of patent rights, any Delaware law purporting to govern the transfer of patent rights would be pre-empted by the federal statute.*[24] *In other words, Delaware law that conflicts with a federal statute or that purports to govern an area of law covered by a federal statute must yield to that federal statute…*"

[24] *See,* e.g., Gonzalez *v.* State*, 207 A.3d 147, 154 (Del. 2019) (explaining federal preemption of state law under the Supremacy Clause of the United States Constitution).*

APPENDIX 13

Abridged Written Evidence of Professor Taft

Statement #1 of 2

"*The identity of the skilled person/team*

22. It has been explained to me that the Patent is to be read through the eyes of the notional person skilled in the art. I have been told that this is someone who is likely to have a practical interest in the subject matter of the invention and has the practical knowledge and experience of the kind of work in which the invention is to be used. He or she lacks inventive capacity but is taken to have the common general knowledge of those working in the field to which the invention relates. I have also been told that the skilled person can be a team.

23. The title of the Patent is 'Lactam-Containing Compounds and Derivatives Thereof as Factor Xa Inhibitors'. As indicated in the field of invention (paragraph [0001] of the Patent), the Patent generally relates to the discovery of antithrombotic compounds that inhibit factor Xa. The Patent states that such compounds are potential therapeutic agents in the treatment of thromboembolic disorders.

24. Drug development requires a team of scientists of various disciplines working together to create a novel therapeutic agent. Bringing a new medication to the market is a laborious, time-consuming, and risky endeavour. The process begins during the initial discovery stage where thousands of compounds are screened for further evaluation. Promising compounds proceed to preclinical testing for additional in vitro and in vivo testing in animals. Once a suitable compound is identified, it proceeds to clinical evaluation in humans in order to establish safety and efficacy for its intended use.

25. By the 1990s, pharmaceutical companies had transformed their approach to research and development in response to rising costs, increased development time, and high rates of attrition as a compound moved along the various phases of development from discovery through clinical testing. The traditional approach of drug discovery that prioritized candidates based on receptor selectivity and potency against a pharmacologic target often resulted in the selection of compounds that had a low probability of becoming a marketed medicine because of poor physicochemical, biopharmaceutical or toxicological properties that development scientists were not able to resolve (Source: S. Venkatash and R.A. Lipper, Role of the Development Scientist in Compound Lead Selection and Optimization. Journal of Pharmaceutical Sciences, 2000, 89:145-154...). One of the primary reasons that compounds failed during development was inappropriate or poor pharmacokinetics.

26. To overcome these challenges, pharmaceutical companies integrated their discovery and development efforts. Under this new paradigm, the pharmacokineticist was brought into a drug development project at the discovery stage to collaborate with the medicinal chemist in order to identify issues regarding absorption, distribution, metabolism and excretion and to help identify compounds that are the best candidates to be developed into a safe and effective medicine.

27. Ideally, the process of drug design and development should provide a delicate balance between the chemistry, pharmacology, and pharmacokinetics of the drug. Pharmacokinetics is a critical determinant of drug action in vivo since it drives the systemic exposure following drug administration. Undesirable pharmacokinetic properties can make a compound with favourable in vitro pharmacologic activity fail during in vivo testing. Additionally, developing new drugs with low potential for drug-drug interactions and patient-friendly dosing schedules places a priority on compounds with specific pharmacokinetic properties. Drug development is a team-based approach and, for the reasons detailed above, a pharmacokineticist is an important part of that team.

28. In my opinion, therefore, I believe that the Patent is directed to a skilled drug discovery team comprised of persons with ordinary skill in various areas of science, including medicinal chemistry and pharmacokinetics. The role and degree of participation of each expert would depend on the phase of development.

29. The skilled pharmacokineticist would have an academic degree of Doctor of Philosophy with specialization in pharmacokinetics (or equivalent) and approximately one year of experience evaluating the pharmacokinetic profiles of small molecule compounds, or an M.S. degree and three or more years of experience.

30. The pharmacokineticist would have a sound knowledge of the principles of absorption, distribution, metabolism, and excretion and the in vitro, in vivo and in silico methods used in pharmacokinetic testing. The pharmacokineticist would be able to calculate the dose needed to achieve target plasma levels based on the pharmacokinetic properties of a compound as well as predict the plasma levels that would be reached after dosing.

31. The pharmacokineticist would have acquired knowledge of pharmaceutics and pharmacology concepts. These include physicochemical properties (e.g., pKa, solubility, permeability), formulation strategies (e.g., immediate release, modified release oral formulations), chemical/physical stability, and pharmacodynamics (the relation between drug concentration at the site of action and effect). The pharmacokineticist would also have knowledge of the analytical methodology used to measure drug concentrations in biological samples such as blood plasma.

32. It has been explained to me that what is important is not my own personal knowledge and views in relation to the issues addressed in this witness statement but those of the relevant skilled person. I believe that except where I have indicated otherwise, the knowledge and views expressed in this witness statement would have been representative of the views of those working in the field in September 2001.

33. The rest of this witness statement is written from the perspective of the skilled pharmacokineticist to which the Patent is directed.

Common general knowledge of the pharmacokineticist

34. It has been explained to me that common general knowledge ('CGK') refers to information that is generally known and generally accepted by the bulk of those working in a particular field as a reliable basis for further work at the relevant time. I have been told that CGK is not limited to the material that the skilled person has memorized but also includes information that is known to exist and would be referred to as a matter of course, if necessary. I also understand that CGK is typically reflected in textbooks and review articles which were widely read or consulted at the time, or shortly afterwards.

35. Except where I have stated otherwise, I believe that the information set out below would have been part of the CGK of the pharmacokineticist working in the field of factor Xa inhibitors in September 2001. Where I use the present tense, it should be understood that my account is of the CGK at that date. Where appropriate, I have provided references to important scientific articles and reviews.

Sources of CGK

36. At the Priority Date of the Patent, the CGK of pharmacokineticist would have been reflected in various publications, including textbooks such as the examples provided below: A. Pharmacokinetics, 2nd Edition (CRC Press, Gibaldi, M & Perrier, D, 1982); B. Clinical Pharmacokinetics: Concepts and Applications, 4th Edition (Williams & Wilkins, Rowland, M & Tozer, T, 1995); and C. Applied Biopharmaceutics and Pharmacokinetics, 4th Edition (Stamford, Connecticut: Appleton & Lange, 1999).

37. When a pharmacokineticist is assigned to a new project, he would first review the published literature and other publicly available information about the topic. In the case of factor Xa inhibition and anticoagulation, the pharmacokineticist would identify the current state of research on factor Xa compounds. He would also review factor Xa pharmacology including the coagulation cascade and learn about the anticoagulants that were on the market such

as warfarin. The pharmacokineticist would work with other members of the research team to identify the goals for the project and formulate a development plan for the project.

Pharmacokinetics (PK) / ADME

38. *Pharmacokinetics may be thought of as the study of the effects of the body on a drug.*
39. *In general, drug therapy involves administering a dose of a medicine that is intended to be delivered to the patient's bloodstream in order for the drug to elicit its pharmacologic activity. After a medicine is administered, the body acts on the drug in various ways. This influences the drug's therapeutic effect. In general, the goal of oral drug therapy is to deliver a sufficient amount of drug to be clinically effective. Drugs delivered orally (the preferred route) have to absorb across from the gastrointestinal ('GI') tract into the bloodstream. Blood is comprised of both cellular (red blood cells, white blood cells, platelets) and liquid components. The liquid portion of blood is called plasma. Besides water, plasma contains proteins, enzymes, antibodies, clotting factors and other components.*
40. *Pharmacokinetics is the science that studies the movement of drugs into, within, and from the body. This is sometimes referred to as drug disposition. Pharmacokinetics involves characterization of drug absorption, distribution, metabolism, and excretion ('ADME'), which taken together describe what happens to a drug after it is administered.*

Absorption

41. *Absorption (the 'A' in ADME) is not a relevant consideration for drugs that are administered directly into the bloodstream (e.g., intravenously). However, the pharmacokinetics of drugs that are administered by other routes, e.g., orally or by subcutaneous injection, can be profoundly affected by the rate and extent of absorption.*
42. *For drugs administered orally as a tablet or capsule, absorption requires that the solid drug particles first dissolve in the GI fluids, then permeate intestinal cells (enterocytes). A schematic depicting the absorption of a drug administered in an oral dosage form (like a tablet) is provided below in Figure 1 [not contained in this judgment], which also shows the drug's movement from administration to the point where it enters the bloodstream (i.e., the systemic circulation....*
43. *Bioavailability (F) is defined as the fraction of administered dose reaching the systemic circulation. In other words, bioavailability reflects the extent of drug absorption. When a medication is administered intravenously, the drug is 100% bioavailable. In order for a drug 1 Although Figure 1 was not published at the Priority Date, the concepts which it illustrates were well-known in September 2001 to reach the systemic circulation following oral dosing, it must first absorb across the intestinal lumen, and this depends on numerous factors including solubility in GI fluids and membrane permeability. Once in the intestinal cell, the drug is susceptible to intestinal metabolism before entering the blood stream. Finally, the fraction of the dose absorbed into the bloodstream must first pass through the liver and escape hepatic metabolism (termed the 'first-pass effect') before becoming systemically available. The dependence of bioavailability on these processes can be described by [a stated equation]....*
44. *In equation (1), fa represents the fraction of the dose absorbed into the intestine, fg is the fraction of dose absorbed into the intestine that escapes intestinal metabolism, and fh is the fraction of dose absorbed into the bloodstream that escapes 'first pass' hepatic metabolism. (Wilkinson, G.R., 'The effects of diet, aging and disease-states on presystemic elimination and oral drug bioavailability in humans' Advanced Drug Delivery Reviews 27 129–159 (1997) at p. 131...). Equation (1) demonstrates that the overall bioavailability of a drug that is orally administered is the product of the fraction of drug that escapes loss in each organ (stomach, intestine, liver).*
45. *The rate of drug absorption can be influenced by a number of factors including the physicochemical properties of the drug, the nature of the drug delivery system, physiologic factors, environmental factors, and the presence of underlying disease. Since drug absorption following oral administration occurs primarily in the small intestine, the rate of*

absorption also depends on gastric emptying time. Gastric emptying time is the time it takes for the stomach contents to empty into the intestine. A number of variables (e.g., exercise, body position, medications) affect this gastric emptying process, but perhaps the most important determinant of gastric emptying is food.

Distribution

46. *Once the drug reaches the bloodstream it has the potential to distribute (the 'D' in ADME) throughout the body to organs and tissues. Most medications need to distribute from the bloodstream to the target organ in order to produce their intended therapeutic effect, but accumulation in off-target sites can lead to adverse effects.*
47. *One of the major factors affecting the distribution is plasma protein binding. Plasma protein binding is a phenomenon where the drug reversibly binds to proteins that exist naturally in human plasma. The main plasma protein responsible for drug binding is albumin, although other plasma proteins (e.g., alpha-1acid glycoprotein, lipoproteins) can bind drugs. As a result, only the free (unbound) form of a drug is able to exit the bloodstream with potential for uptake by organs and tissues. Thus, plasma binding potentially limits the distribution of drug in the body, and the unbound plasma concentration is considered to be reflective of the concentration of drug available at the site of action.*
48. *The extent to which the drug is distributed outside the plasma is described by its volume of distribution, which is discussed further below.*

Metabolism and Excretion

49. *There are two main clearing organs in the body: the liver and kidney. The liver is primarily responsible for drug metabolism (the 'M' in ADME). Metabolism is the process by which the body modifies the molecular structure of the drug, usually resulting in a form that is inactive or more easily removed from the body (in the form of metabolites).*
50. *The kidney is primarily responsible for excretion (the 'E' in ADME). Excretion is the process by which the drug and/or its metabolites are physically removed from the body, usually either in the bile or in urine.*
51. *Not all drugs have the same ADME characteristics. Collectively, these characteristics define the pharmacokinetic profile of a drug, which consists of various parameters that provide information about a drug's absorption, distribution, metabolism, and excretion. The pharmacokinetic profile of a drug is a critical determinant in its development into a medicine because it impacts the design of a dosing regimen; that is, how much drug should be administered (i.e., the dose) and how often (i.e., the dosing frequency). The pharmacokineticist would have in depth knowledge of all aspects of ADME for drugs.*
52. *For most drugs, the aim of an appropriate dosing regimen is to maintain the drug concentration at the level required for efficacy, but below the level at which toxicity becomes a problem.*
53. *Controlling the pharmacokinetic parameters of a new compound is critical to the success of any drug discovery effort. An orally active compound needs to reach the blood in sufficient concentration and remain in the body long enough to interact with the biological target.*

Pharmacokinetic Studies

54. *A drug's pharmacokinetic profile can be determined using in vitro, in vivo, and in silico methods. In vitro methods are laboratory tests conducted in an environment outside of the body such as in test tubes. In vivo studies are conducted in animals or humans, and typically require greater quantities of the drug for testing. And in silico approaches are those that involve application of computer modelling and simulation.*
55. *In vivo pharmacokinetic studies typically involve administering the drug, then measuring plasma concentrations at various time points. Once these plasma samples are collected and analyzed, the pharmacokineticist plots a graph showing plasma concentration changes over*

time. A typical plasma concentration-time profile for an orally administered drug is shown in Figure 2 [not contained in this judgment], which identifies key indicators of drug exposure: Cmax (labeled peak concentration in the figure) and AUC....

56. *The maximum or peak concentration of drug measured in plasma after dosing is called the Cmax. The area under the curve ('AUC') is a measure of how much drug is exposed to the body (commonly referred to as systemic exposure). AUC is typically calculated from time 0 (when the dose is administered) to the time when the dose is completely eliminated from the body.*

Therapeutic Range

57. *As explained above, for most drugs, the aim of an appropriate dosing regimen is to maintain the drug concentration at the level required for efficacy, but below the level at which toxicity becomes a problem. The dosage regimen must therefore be designed such that it does not result in concentrations above the safe maximum or below the desired minimum.*

58. *The therapeutic range refers to the target window of plasma concentrations between a maximum tolerated concentration ('MTC') and the minimum effective concentration ('MEC'). This window is depicted as the horizontal dashed lines in Figure 2 [not shown in this judgment]. The width of the therapeutic window and the speed of drug elimination from the body govern how much drug a patient should receive (i.e., the dose) and how often (the dosing frequency), as illustrated in Figure 3 [not shown in this judgment]....*

Pharmacokinetic Profile and Parameters

59. *The key pharmacokinetic parameters used to characterize drug absorption, distribution, metabolism, and excretion are volume of distribution ('VD'), clearance ('Cl'), and elimination half-life ('t1/2'). Together these parameters make up the pharmacokinetic profile of a compound along with another important parameter, bioavailability ('F'). The pharmacokineticist would have in depth knowledge of all aspects of VD, Cl, and t1/2 as well as F. A. Volume of distribution (VD): describes the extent to which a drug leaves the bloodstream and distributes elsewhere in the body. VD (in liters, L) is a proportionality constant relating the amount of drug in the body as compared to its concentration in the plasma, as defined by [a stated equation]...(2) VD reflects the extent of distribution in the body, and it depends on the chemical nature of the drug (lipophilic vs. hydrophilic) and the relative binding of drug in plasma compared to tissue. VD is considered an apparent volume of distribution because it does not represent an actual volume. Although the total amount of water in a person's body is approximately 42 L, some medications have VD values in excess of 1000 L. The larger the VD, the greater the distribution throughout the body and the lower the plasma concentration for a given dose. The dose needed to produce target plasma concentrations (e.g., Cmax) depends on VD. Drugs with larger VD will distribute more into tissues, with less drug remaining in the plasma. This will require greater doses to achieve target plasma concentrations. B. Clearance (Cl): Cl is a critical determinant of what happens to a drug in the body, because it is the parameter (along with bioavailability) that determines the systemic exposure (AUC) following oral dosing, as described by [a stated equation]...(3) Clearance is a collection of processes by which the body removes the drug from the body, primarily through metabolism and excretion. Substances can be cleared from the body by various organs, but the liver and kidney are the most important. Mathematically, Cl represents the rate of drug elimination from the body as compared to its plasma concentration. It is defined as the fluid volume of plasma that is completely cleared of drug per unit time (usually L/h or mL/min). For example, for a drug with a Cl of 30 mL/min, this means 30 millilitres of plasma are completely cleared of drug every minute. Drugs with higher Cl will have lower systemic exposure (AUC) for a given dose, meaning lower drug levels in the plasma after a drug is administered. Compounds with high clearance from the body may therefore not remain in the blood long enough to effectively reach their target. The clearance of many drugs is restricted by plasma binding and is directly proportional to the fraction of unbound drug in the plasma. These drugs are referred to as 'low extraction*

ratio' drugs. Extraction ratio is the ratio of a drug's metabolic Cl and hepatic blood flow (90 L/hr in humans). This ratio ranges between 0 (no metabolism or very low Cl) up to 1 (when Cl is so high it becomes limited by liver blood flow). As discussed in paragraph 43, hepatic metabolism can limit oral bioavailability through the 'first pass effect'. Thus, drugs with a large metabolic Cl will have low oral bioavailability, because the fraction of the dose absorbed into the bloodstream that escapes first pass metabolism (fh) is low. This is illustrated by [a stated equation]...(4) For example, a compound with a metabolic Cl of 70 L/hr in humans has an extraction ratio of ~ 0.78, indicating that it is efficiently extracted from the bloodstream by the liver. Based on equation 4, fh equals 0.22 or 22%. This means that the oral bioavailability of this compound cannot exceed 22%, even if the compound is completely (100%) absorbed into the bloodstream after oral dosing. C. Half-life (t1/2): t1/2 represents the period of time that it takes for the total amount of that drug in the body to be reduced by one half (50%). Half-life reflects how rapidly plasma concentrations decline after a drug is administered. The longer the t1/2, the longer it takes for the drug to be eliminated from the body. A drug's t1/2 depends on the drug's VD and Cl (two independent pharmacokinetic parameters) according to the following Equation (5). This shows that the lower the t1/2, the faster the drug is eliminated from the body, and the more quickly plasma concentrations are reduced, which will result in the need for more frequent dosing of the drug....

60. *Drugs are commonly prescribed to be taken on multiple dose regimens with a particular dosing frequency (e.g., take this twice daily for 2 weeks). With multiple dosing, plasma concentrations fluctuate between the 'peak' or maximum concentration (Cmax) and 'trough' or minimum concentration (Cmin), as illustrated in Figure 4 [not shown in this judgment]. The degree of fluctuation between peak and trough plasma concentrations is also known as a drug's peakto-trough characteristics, and t1/2 determines the extent to which plasma concentrations will fluctuate in a patient receiving multiple doses. By eliminating more slowly from the body, a drug with a long t1/2 produces less fluctuation of plasma levels over time, and this allows for less frequent dosing of the drug....*

Pharmacokinetic Testing

61. *Before a compound under development can be tested in humans, safety and proof of concept must be established through preclinical studies. Preclinical drug development involves using a combination of methods to assess physicochemical, pharmacologic, pharmacokinetic and toxicologic properties in order to screen out for further evaluation compounds with the optimal balance of potency, selectivity, safety and pharmacokinetics. This can be done both by conducting in vitro experiments and in vivo pharmacokinetic studies.*

62. *In vitro experiments can provide important information to help assess the pharmacokinetic properties of a particular compound under study. For example, in vitro studies to characterize drug solubility and permeability provide information regarding the potential for suitable absorption into the bloodstream following oral dosing.*

63. *In vivo pharmacokinetic studies are used to determine key pharmacokinetic parameters (Cl, VD, t1/2) and to assess the bioavailability of a test compound after oral administration. When these experiments are conducted in non-human animals such as rodents (mice, rats), dogs and monkeys, they are referred to as preclinical studies.*

64. *Advances in combinatorial chemistry resulted in production of enormous numbers of compounds with potential pharmacologic activity. The large number of molecules being generated during the drug discovery process and the need to balance potency with pharmacokinetics to achieve valuable and developable drugs required that higher throughput (i.e., faster testing) methods be used for rapidly screening candidates for absorption, distribution, metabolism, and excretion properties. In addition to high throughput in vitro methods, cassette or 'N-in-One' dosing emerged as a tool that enabled pharmaceutical scientists to rapidly screen large numbers of candidate compounds by administering them simultaneously to a single animal (White 2001...).*

65. The above-mentioned tools and techniques were known in the art before the Priority Date. Moreover, as noted in the figure below [not shown in this judgment], pharmacokinetic and metabolic studies were integrated across all stages of drug development at that time. Pharmacokinetic and biotransformation studies are essential for the selection of the optimum compound from a series of candidates (Bozler and Schmid 1989...)....

66. It was not common for drugs with a long t1/2 to have both a low Cl and VD. The figure below [not shown in this judgment] shows values of Cl and VD for some of the most common drugs at the time....

Key attributes of a factor Xa inhibitor

67. After joining a drug development project team, a pharmacokineticist would first review the published literature and consult with other members of the research team to acquire knowledge about antithrombotic drug therapy. The skilled pharmacokineticist would therefore have been aware that many pharmaceutical companies were undertaking drug discovery efforts to identify new anti-thrombotic agents that could be administered orally. At the Priority Date, warfarin was the only orally effective anticoagulant available. Warfarin, an indirect acting inhibitor of vitamin K-dependent clotting factors, suffers from a slow onset of action and numerous drug:drug and drug:food interactions. Patients treated with warfarin require careful monitoring and dose adjustments to avoid bleeding, a serious adverse effect. Consequently, development of a direct acting, orally available anticoagulant with less risk of bleeding was a long sought-after goal.

68. At a high level, the coagulation or clotting cascade involves two 'pathways' leading to the formation fibrin, which is the basis of all blood clots. These are referred to as the intrinsic and the extrinsic pathway.

69. Drug discovery efforts initially concentrated on compounds that inhibited generation of thrombin because of its important role in the conversion of fibrinogen to fibrin as well as inducing platelet aggregation (Hiryama 2002...). Because of safety and efficacy concerns with direct thrombin inhibition, subsequent development efforts focused on inhibition of factor Xa as an approach to inhibit thrombin generation but not inhibit any of its other functions (Rai 2001...).

70. Factor Xa is at the final convergence point of the intrinsic and extrinsic coagulation pathways and is the active enzyme in the prothrombinase complex that converts inactive prothrombin to active thrombin, which ultimately leads to blood clotting. By the Priority Date, pharmaceutical companies across the globe were pursuing factor Xa inhibitors in their quest to develop new anticoagulant medicines. The site of action for a factor Xa inhibitor is the plasma because that is where the factor Xa enzyme is located. For direct-acting anticoagulants like factor Xa inhibitors, it is desirable to maintain plasma concentrations within the therapeutic window. Too much drug in the bloodstream (i.e., high Cmax) can lead to potentially fatal bleeds, whereas too little drug (low Cmin) may not prevent potentially fatal blood clots.

71. The published literature included articles from researchers at Daiichi (Nagahara 1994...), Rhone-Poulenc Rorer (Pauls 2001...), Berlex (Light 2001...) and others describing their factor Xa inhibitor development programs.

72. Although these companies were testing different chemical families, their goal was to find compounds that possessed the following characteristics: potent factor Xa inhibition, selectivity versus other related serine proteases, suitability for oral dosing, and favorable pharmacokinetic properties. By 2000, a number of preclinical development programs had identified orally bioavailable inhibitors with demonstrated activity in animal models of thrombosis, but it remained to be determined how factor Xa inhibitors would perform under clinical testing in humans (Vacca 2000...).

73. As noted in Zhu and Scarborough (2000)...finding a clinically viable oral factor Xa inhibitor required a very careful and systematic approach to optimize in vitro potency, specificity, and physicochemical properties in order to achieve both a good pharmacokinetic profile (high oral bioavailability and long t1/2) and antithrombotic efficacy. The authors noted that

development scientists need to balance the ideal properties of a compound from both an efficacy perspective as well as a pharmacokinetic perspective.

74. *In summary, by the Priority Date, research laboratories throughout the world were actively seeking to discover factor Xa inhibitor compounds that could be developed into safe and effective antithrombotic medicine. While potency and selectivity were important considerations in candidate selection, research programs recognized that compounds also needed to possess favourable pharmacokinetic properties to be successfully developed into a drug. This is reflected in the scientific literature, including a publication by Berlex Biosciences, stating that its lead factor Xa compound (CI-1031) was chosen for clinical evaluation based upon factors including pharmacokinetics (Light 2001...). In terms of favorable pharmacokinetic properties, the literature showed that factor Xa researchers were searching for inhibitor compounds with suitable oral bioavailability, low clearance, and prolonged t1/2 (Zhu and Scarborough 2000, Zhu 1999, Pinto 2001...). Therefore, the skilled pharmacokineticist was an important part of a drug discovery team tasked with screening factor Xa inhibitors to help identify the most promising compounds to move forward for further development and evaluation.*

The Application and apixaban

75. *A skilled pharmacokineticist reading the Application on the Priority Date in light of his/her CGK would have understood the following.*

76. *The Application is entitled 'Lactam-containing compounds and derivatives thereof as Factor Xa Inhibitors'. As indicated in the field of invention on page 1 of the Application, the invention generally relates to compounds that inhibit trypsin-like serine protease enzymes, particularly factor Xa. The Application states that such compounds are anticoagulant agents for use in the treatment of thromboembolic disorders (like strokes and heart attacks).*

77. *The background of the invention section on pages 1 to 6 of the Application, explains that many different factor Xa inhibitors had already been discovered, and that the inventors were looking for more efficacious and specific factor Xa inhibitors.*

78. *The role and importance of factor Xa in the coagulation cascade is discussed in the Application on pages 5 and 6. The basic premise was that clotting could be reduced by inhibiting the factor Xa enzyme (which is located in the plasma) which in turn would directly interrupt the blood coagulation system.*

79. *The vast majority of the rest of the Application describes the chemical structures and synthesis of a genus of lactam-containing factor Xa inhibitors. This would be of greater interest to the medicinal chemist on the skilled team than the pharmacokineticist. However, the skilled pharmacokineticist would have been particularly interested in the advanced research objectives listed on page 6 of the Application. The skilled pharmacokineticist would recognize, on the basis of these objectives, that the project had gone beyond merely identifying compounds that interacted with the target to identifying compounds with the desired pharmacological profile. The Application teaches that it was desirable to discover factor Xa inhibitors having advantageous and improved characteristics, in categories (a) to (f) in particular, which would have been understood by the skilled pharmacokineticist to include an overall sought-after pharmacokinetic profile: 'Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors. In addition, it is also desirable to find new compounds with improved pharmacological characteristics compared with known factor Xa inhibitors. For example, it is preferred to find new compounds with improved factor Xa inhibitory activity and selectivity for factor Xa versus other serine proteases (i.e., trypsin). It is also desirable and preferable to find compounds with advantageous and improved characteristics in one or more of the following categories, but are not limited to: (a) pharmaceutical properties (e.g., solubility, permeability, and amenability to sustained release formulations); (b) dosage requirements (e.g., lower dosages and/or once-daily dosing); (c) factors which decrease blood concentration peakto-trough characteristics (e.g., clearance and/or volume of*

distribution); (d) factors that increase the concentration of active drug at the receptor (e.g., protein binding, volume of distribution); (e) factors that decrease the liability for clinical drug-drug interactions (e.g., cytochrome P450 enzyme inhibition or induction); (f) factors that decrease the potential for adverse side-effects (e.g., pharmacological selectivity beyond serine proteases, potential chemical or metabolic reactivity, and limited CNS penetration); and, (g) factors that improve manufacturing costs or feasibility (e.g., difficulty of synthesis, number of chiral centers, chemical stability, and ease of handling).' (Page 6, lines 6-35)

80. *The Application teaches that it was desired and preferred to discover factor Xa inhibitors capable of being administered at low doses and/or once daily dosing and that it was also desired to achieve an increase in the concentration of active drug at the receptor (objectives (b) and (d)). Factor Xa inhibitors exert their effect in the blood, therefore, to achieve these objectives, it is desirable to maintain suitably high plasma concentrations and a low VD.*

81. *The Application teaches that it was also desired and preferred to discover factor Xa inhibitors with decreased peak-to-trough characteristics (objective (c)). Decreased peak-totrough characteristics require a long half-life; therefore, the Application is teaching that the desired pharmacokinetic profile must also simultaneously include an even lower Cl. This is because, although VD and Cl are independent pharmacokinetic parameters, they are interrelated and related to t1/2 by equation 2 shown below. As the equation below shows, in order for a low VD drug to also have a long t1/2, it must have an even lower Cl....*

82. *For example, assuming a target t1/2 of 10 hours, the Cl of the compound would need to be at least an order of magnitude (i.e., more than 10-fold) lower than VD in order to meet the objectives of less frequent dosing and reduced fluctuation between peak and trough. Thus, in order for a compound with a relatively low VD (e.g., 25 L) to have a t1/2 of approximately 10 hr, the Cl would need to be less than 2 L/hr.*

83. *For the following reasons, it is my opinion that the Application's disclosure goes further. It teaches the skilled pharmacokineticist that a pharmacokinetic profile simultaneously comprising both a low VD and an even lower Cl is not only necessary but also ideal given the stated research objectives: A. Not only is the simultaneous occurrence of both a low VD and an even lower Cl a pharmacokinetic profile that can achieve the above objectives identified on page 6 of the Application, but it also provides improvements and advantages with respect to the following additional research objectives identified on page 6 of the Application. B. When a compound has a low VD, the majority of the absorbed dose is confined to the bloodstream after administration, with limited drug distribution to and accumulation in off-target tissues. A factor Xa inhibitor with low VD would achieve the objective of increasing the concentration of drug in the bloodstream (where it exerts its intended effect against the receptor) while also decreasing the potential for adverse side-effects by restricting drug access to other areas of the body. C. A drug with a low VD requires a lower dose to achieve a target plasma concentration. As it would be highly desirable to deliver a drug as a solid oral dosage form, lower dosage requirements can help overcome factors that can impair drug absorption and limit bioavailability, such as aqueous solubility. For solid oral dosage forms, the compound must first dissolve in gastrointestinal fluids in order to be able to absorb across the intestinal cell, and this process depends on solubility. If the dose required to reach effective plasma levels is high, it may be difficult to develop an effective oral formulation due to solubility limited absorption. Since compounds with low VD tend to be hydrophilic, the lower dose required to produce target plasma levels would likely not be impacted by solubility limitations. D. In addition, this profile would reduce or eliminate the impact of pre-systemic metabolism on oral bioavailability. As depicted above in Figure 1 [not shown in this judgment], a drug that is absorbed from the intestine into the blood after oral dosing is carried by the portal blood system through the liver, where it must escape hepatic metabolism before it circulates through the heart and becomes systemically available. A low Cl drug is not as susceptible to this 'first-pass effect', because of its low extraction ratio. For example, a drug with a Cl of 3 L/hr has a predicted extraction ratio in humans of 0.03, meaning that 97% of drug that is absorbed into the bloodstream reaches the systemic circulation.*

84. *The skilled pharmacokineticist would therefore have concluded from the Application that the inventors sought potent and specific inhibitors of factor Xa that also had the ideal*

pharmacokinetic profile that simultaneously comprised both a low VD and an even lower Cl.

85. *As mentioned above, the teaching of the majority of the rest of the Application would be of greatest interest to the medicinal chemist. While the synthesis of a number of compounds is provided in the examples, no pharmacokinetic data specific to any one compound is provided.*

86. *However, the skilled pharmacokineticist would have considered it significant that Example 18, which I understand to be apixaban, was the only exemplified compound in the Application to have been scaled up and made in gram quantities, which would have been enough material to permit preclinical testing in animals to establish the compound's pharmacokinetic profile (see page 222 of the Application). Further, this would have singled out Example 18 to the skilled team as being a compound that the inventors were particularly focussed on, especially since no other compound was disclosed to have been made in such quantities. This is the type of information that the medicinal chemist would have told the pharmacokineticist.*

87. *The skilled pharmacokineticist would also have considered it significant that Example 18 is the only example in the Application to have two crystallization purification steps. The inventors initially obtained 2.5 grams of apixaban (which is already a large amount in this context), and then conducted a recrystallization to obtain another 0.57 grams of apixaban, for a total yield of 3.07 grams. This would have told the skilled pharmacokineticist that the inventors were trying to synthesize large quantities of highly pure apixaban for advanced testing.*

88. *My laboratory has collaborated with the pharmaceutical industry on drug development projects during my tenure at Long Island University. In several cases, we were contracted to carry out preclinical pharmacokinetic screening experiments on a series of investigational compounds. Since the sponsor company had a limited supply of each compound available, we were provided only the minimum amount of each compound that was needed to run the experiments. In one project (unpublished), we tested investigational compounds in experiments that required less than 10 micrograms of test material. Although we conducted these studies in triplicate and at different doses, we were provided with less than a milligram of each compound to conduct the experiment. In another project that we published (Tamhane 2010...), we evaluated the renal excretion and protein binding of VX-702, a compound under development by Vertex. The experiments we performed required less than two milligrams of compound.*

89. *The amount of material needed to perform an in vivo preclinical pharmacokinetic experiment depends on the goal of the experiment and the species of animal tested. An initial screening experiment would likely involve administration of a low dose (e.g., 1 mg/kg) of one of more compounds to a single rat (body weight ~ 0.25 kg). Requiring a small amount of test material (< 1 mg in this example), this type of experiment would enable researchers to evaluate a number of compounds and to identify promising candidates that merit further pharmacokinetic evaluation. These most promising compounds would proceed to in vivo testing in dogs (body weight ~ 10 kg), where the animal would receive an oral dose (e.g., 5 – 10 mg/kg) of test material (Light 2001 at Table 13...Pauls 2001 at Table 13...). An experiment of this type would require significantly more material (50 mg in this example) and may involve more than one test animal. A compound that shows a favorable pharmacokinetic profile in this experiment would likely be subjected to more extensive preclinical testing across different species in order to assess the relationship between dose and systemic exposure relationship (requiring experimentation at different doses) and to screen for potential drug:drug interactions. Thus, as a promising drug candidate advances through preclinical development, the amount of material needed to carry-out necessary pharmacokinetic experimentation increases substantially.*

90. *Example 18 does not expressly state that the scale up was conducted in order to prepare material to permit preclinical testing in animals to establish apixaban's pharmacokinetic profile. However, the skilled pharmacokineticist would have known that lead compounds are subjected to extensive testing. Typically, there are a number of in vitro tests which are carried out, including tests for potency and selectivity. There are also in vivo experiments*

in both small (such as rats, dogs, and rabbits) and larger animals (such as primates), to evaluate the compound's pharmacokinetic properties, antithrombotic efficacy, and toxicity.

91. *In addition, more than one set of pharmacokinetic experiments are typically conducted, and scientists need to develop and validate an analytical method to measure the plasma levels observed in the animals after dosing. This is why the skilled pharmacokineticist (and skilled team as a whole) would have considered the multi-gram scale up of Example 18 (apixaban) to be so significant and understand that it had been scaled up for extensive study, including for its pharmacokinetic properties.*

92. *Based on the amounts made of some of the other compounds, the skilled pharmacokineticist would have reasoned that some of those examples may have been tested initially for their pharmacokinetic properties as well. However, no other example is scaled up to multi-gram quantities. This serves to underscore why the skilled pharmacokineticist would have found it so remarkable that apixaban was scaled up to such a greater degree than the other compounds. It suggests that apixaban's initial pharmacokinetic results were quite promising and larger-scale studies were required.*

93. *Moreover, the skilled pharmacokineticist would have understood from the research objectives set out on page 6 of the Application that the inventors had advanced drug discovery goals in mind in their search to find a novel anticoagulant that was capable of being studied in the clinic and used as a drug. When Example 18 is read in context, the skilled pharmacokineticist would have concluded that apixaban had been scaled up for indepth evaluation for its potential as a medicine.*

94. *As stated above, the skilled pharmacokineticist would have observed that the discussion on page 6 of the Application is particularly focused on the discovery of factor Xa inhibitors with the pharmacokinetic profile that the Application teaches is ideal given the stated research objectives. That is, a pharmacokinetic profile that would allow the inhibitors to be given in low dosages, while (i) maximizing concentration in the bloodstream (where factor Xa is located and where the drug exerts its therapeutic effect), (ii) minimizing accumulation in off-target tissues (where adverse side effects can manifest),(iii) decreasing peak-totrough characteristics, and (iv) providing other advantages listed above in terms of other categories set out on page 6. The skilled pharmacokineticist would have understood such compounds to be exceptional among factor Xa inhibitors.*

95. *The skilled pharmacokineticist would have observed that the discussion on page 6 of the Application is particularly focused on the discovery of factor Xa inhibitors with a pharmacokinetic profile aligned to the stated research objectives, namely, a pharmacokinetic profile that has both a low VD and an even lower Cl.*

96. *Given these disclosures in the Application, namely the stated research objectives on page 6 and the gram quantities of apixaban that was made in Example 18, which suggest that initial pharmacokinetic results were sufficiently promising to move to larger-scale studies, and given that no other compound was disclosed to have been made in such quantities, it is my opinion that the skilled pharmacokineticist would have a positive reason to believe that apixaban has the desired pharmacokinetic profile of both a low VD and an even lower Cl.*

97. *The skilled pharmacokineticist would, therefore, have understood that apixaban's pharmacokinetic profile, as taught in the Application, would result in the following benefits for the treatments contemplated by the claims of the Patent: A. increased concentration of drug at the receptor (factor Xa is located in the plasma), meaning the dose tends to stay in the bloodstream where the drug works; B. retention of the drug in the plasma for a longer period of time, which would not only allow for lower dosages (and also mean the dose would tend to stay in the bloodstream), but also provide the benefits of decreased peak-to-trough characteristics (i.e., to avoid bleeds and clots) and the potential for once daily dosing; C. reduced pre-systemic metabolism on oral bioavailability because low Cl drugs are not as susceptible to the so-called 'first-pass effect'; and D. decreased potential for adverse side-effects by keeping the drug out of off-target tissues where adverse side-effects can manifest.*

98. *Therefore, it would have been plausible to the skilled pharmacokineticist at the Priority Date that apixaban was a factor Xa inhibitor (having the desired pharmacokinetic properties) and effective for the treatment of thromboembolic disorders.*

WO 131 AND APIXABAN

99. I have been asked by McCann FitzGerald LLP to give my opinion on whether it would have been plausible to the skilled pharmacokineticist reading the Patent in the light of the CGK at the Priority Date that apixaban, or any other compound disclosed in the Patent, would have improved characteristics compared to compounds disclosed in the prior art, including in WO 131.

100. I have also been asked by McCann FitzGerald LLP to give my opinion on whether it would have been plausible that apixaban is a compound for use in treating a claimed thromboembolic disorder.

101. I have identified the person skilled in the art and the CGK above.

102. Like the Patent, WO 131 indicates that the inventors were involved in a drug discovery project and teaches the skilled pharmacokineticist what the inventors' goals were. At page 2, it states that 'efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders'. The goal of the project is simply stated as follows: 'It is thus desirable to discover new factor Xa inhibitors'. No other research goals are stated. This is a stark difference from the Application, which describes different and more advanced research objectives, with the inventors looking to find compounds with a particular pharmacokinetic profile. These properties on page 6 of the Application would particularly stand out to the skilled pharmacokineticist.

103. There is no equivalent disclosure in WO 131 to the objectives described on page 6 of the Application. Further, the skilled pharmacokineticist would understand that apixaban was selected to be made in greater quantities (as per Example 18) because it met those objectives.

104. As mentioned above, the skilled pharmacokineticist would have recognized that the Patent (and Application) discloses the synthesis and purification of apixaban in Example 18. The skilled pharmacokineticist would have considered it significant that apixaban was the only exemplified compound in the Application to have been scaled up and made in enough quantities to permit preclinical testing in animals to establish its pharmacokinetic profile (see paragraphs 86 to 88 above). Accordingly, when Example 18 is read in context, the skilled pharmacokineticist would have concluded that apixaban had been scaled up for indepth evaluation for its potential as a medicine.

105. As stated above, the skilled pharmacokineticist would have observed that the discussion in paragraph [0019] of the Patent (page 6 of the Application) is particularly focused on the discovery of factor Xa inhibitors with a pharmacokinetic profile aligned to the stated research objectives, namely, a pharmacokinetic profile that has both a low VD and an even lower Cl.

106. Read in conjunction with example 18 and the conclusion that apixaban had been scaled up for in-depth evaluation for its potential as a medicine, the skilled pharmacokineticist would have understood the disclosure at [0019] of the Patent (page 6 of the Application) as not only describing a particular pharmacokinetic profile as required for a more effective factor Xa inhibitor but as describing the actual pharmacokinetic profile for (at least) apixaban. This pharmacokinetic profile will make a more effective compound for treating a thromboembolic disorder.

107. For these reasons, it is my opinion that the Application and the CGK would have provided the skilled pharmacokineticist with a positive reason to believe that apixaban would have improved characteristics in the categories specified on page 6 of the Application (see paragraph 79 above) compared to compounds disclosed in WO 131.

108. Therefore, it would have been plausible to the skilled pharmacokineticist at the Priority Date that apixaban was a factor Xa inhibitor with improved pharmacokinetic properties and effective for the treatment of thromboembolic disorders."

Statement #2 of 2

"*16. I note that in paragraph 5.11, Dr. Wargin has not defined what he means by 'high variability'. All drugs will have intersubject variability (and intrasubject variability too) and it is not clear to me what Dr. Wargin means by 'high' in that context.*

17. I disagree with the definition or explanation of elimination half-life (t1/2) provided in paragraph 5.12. Under the conditions of first order elimination (where the elimination rate is proportional to the plasma concentration of the drug), the elimination t1/2 is constant (independent of plasma concentration). It is defined as the time it takes for plasma concentrations to decline by 50%. Most medications undergo first order elimination at clinically relevant concentrations, and this makes t1/2 a useful parameter to predict how quickly a drug is elimination from the body after dosing, how much accumulation will occur with a multiple dosing regimen, and the degree of fluctuation between peak and trough plasma levels at steady state.

18. I find the definition of Drug-Drug Interactions ('DDI') at paragraph 5.14.1 to be confusing and simplistic. I believe the issue with DDI is whether co-administration of two or more medications alters the systemic exposure of any of them. Systemic exposure is reflected in AUC. The most important pharmacokinetic DDIs involve altered clearance (clearance and elimination are not synonymous although Dr. Wargin uses the terms interchangeably in his statement).

19. I agree with Dr. Wargin at paragraph 7.1.2 in so far as that the list of characteristics at paragraph 7.1 would be desirable characteristics for any drug. However, in the context of developing a factor Xa inhibitor, a skilled pharmacokineticist would recognize from these characteristics what the ideal profile would be.

20. I disagree with Dr. Wargin's conclusion at paragraph 7.2 for the reasons stated previously.

21. I disagree with Dr. Wargin's conclusion at paragraph 7.3. See my comment at 9 above - armed with WO652 and what it teaches, a skilled pharmacokineticist could conduct routine testing with Example 18 and evaluate its pharmacokinetic profile using the experimental tests Dr. Wargin describes in his statement."

APPENDIX 14

Abridged Written Evidence of Professor Thomas

Statement #1 of 2

"*INTERPLAY BETWEEN EUROPEAN PATENT LAW AND US LAW*

26. *Article 4.A(2) of the Paris Convention for the Protection of Intellectual Property (PC) provides the starting point for determining whether a patent applicant has established a priority date. That provision reads in pertinent part that '[a]ny filing that is equivalent to a regular national filing under the domestic legislation of any country of the Union ... shall be recognized as giving rise to the right of priority.' Article 87(1) of the European Patent Convention (EPC) similarly provides that '[a]*ny person who has duly filed ... an application for patent ... shall enjoy ... a right of priority.*' These international agreements provide that the right to claim priority from an earlier patent application is an independent property right owned by the applicant(s) who has/have duly filed that earlier application. This right is separate from the issue of who owns the substantive rights in the invention, e.g. who is entitled ultimately to be granted a patent. In accordance with these international agreements, the right to claim priority vests solely with those named as applicants on the priority application, and their successors in title.*

27. *The United States is a party to the PC. US165 is a US provisional patent application. As such, the question of whether BMS has a valid right to claim priority to US165 requires assessment of whether prior to the filing date of the PCT Applrcation, BMS Company was successor in title to US165 for the purposes of filing the European patent application.*

APPLICABLE LAW- U.S. FEDERAL OR STATE LAW

28. *There are two court systems in the United States: federal courts, which operate under the federal laws of the US, and state courts, which operate under the laws of each respective state. All cases arising under US patent laws must be heard in a federal court.*

29. *Where applicable, the federal court will apply both state law and federal patent Jaw where issues of state law are intertwined with federal patent law issues. For example, in* Tyco Healthcare Group LP *v.* Ethicon Endo-Surgery*, 587 F.3d 1375 (Fed. Cir. 2009), the Federal Circuit applied Delaware contract law to construe an assignment allegedly transferring ownership of the asserted patents to the plaintiff, Tyco Healthcare. The Federal Circuit ultimately concluded that Tyco Healthcare had not shown that it owned the patents that it had asserted and therefore dismissed the case for lack of standing.*

30. *In the US, state law governs the ownership of property (including intellectual property) and the interpretation of contracts. Therefore, the question of who has legal title to a patent is a matter of state law (*Enovsys LLC *v.* Nextel Commc'ns, Inc.*, 614 F.3d 1333, 1342 (Fed. Cir. 2010)).*

31. *Notwithstanding the general applicability of state law to questions regarding ownership of property and the interpretation of contracts, federal law governs the way in which an assignment of patent rights (including the right to clalm priority) can be made.*

32. *The leading case in this area,* Board of Trustees of the Leland Stanford Junior University *v* Roche Molecular Systems, Inc, *583 F.3d 832,841 (Fed. Cir. 2009), aff'd, 563 U.S. 776, 131 S. Ct. 2188, 180 L. Ed. 2d 1 (2011), summarized the situation as follows:*

> *'[T]*he question of who owns the patent rights and on what terms typically is a question exclusively for state courts ... However, this rule has exceptions; the

> question of whether contractual language effects a present assignment of patent rights, or an agreement to assign rights in the future, is resolved by Federal Circuit law.*'*

33. *There is therefore an overlap between state law and federal law regarding the transfer of patent rights and the two must be considered together in order to determine whether a particular purported transfer of patent rights is valid.*

FEDERAL LAW - ASSIGNMENT OF PATENT RIGHTS

34. *Any transfer of the rights in present or future inventions or in or under present or future patents or patent applications under US law is governed by the combined effect of:*

> *a. The state law of the agreement by which the rights in the same are said to be transferred; and*
> *b. Federal law.*

35. *The applicable state law, here Delaware law, would govern the interpretation of particular contractual elements of an assignment. My analysis below focuses on the federal laws that govern an assignment of patent rights.*

An instrument in writing

36. *Federal law, arising from the United States Code, governs the transfer of patent rights. lt stipulates that these rights must be assigned by an '*instrument in writing*' (35 USC§ 261). The relevant provision is:*

> *'*Applications for patent, patents, or any interest therein, shall be assignable in law by an instrument in writing'.

37. *The statute does not stipulate the form or the contents of the written instrument, and courts have held that this statute '*imposes minimal requirements for such [an] assignment.*'* Software Rights Archive LLC *v* Google Inc.*, No. CIV.A. 2:07-CV-511, 2009 WL 901361, at *4 (E.D. Tex. Mar. 31, 2009).*

38. *The District Court in* Schwendimann *v.* Arkwright Advanced Coating, Inc., No. CIV. *11-820 ADM/JSM, 2012 WL 928214, at *6 (D. Minn. Mar. 19, 2012) explained that the '*relevant inquiry is solely whether the purported assignment is in writing' *and it went on to look at the meaning of '*an instrument in writing*':*

> *'*Without any express statutory definition, what is meant by an "instrument in writing" must be determined by reference to its ordinary meaning. *Asgrow Seed Co*. v *Winterboer*, 513 U.S. 179, 197 (1995) ('When terms used in a statute are undefined, we give them their ordinary meaning' J. The ordinary meaning of 'owning is an intentional reduction to tangible form.*'* *(emphasis added)*

39. *Based on the information in the Documents, there is no purported tangible form of an assignment. The only information relied on is a supposed internal policy of patent ownership in an internal BMS Company email chain in October 2001. These showed that BMS Company had a right to call for such a transfer. There is no evidence or statement to support the proposition that this right was ever exercised prior to the filing date.*

COMMENTS ON THE EXPERT REPORT OF THE LATE JUSTICE HOLLAND

40. *I have had the opportunity to review the Holland Report which I understand was relied upon by BMS Ireland in the Italian proceedings. While I have the greatest respect for the late Justice Holland, I strenuously disagree with his conclusion that '*BMS could be

characterized as the beneficial owner of the earlier filed patent application.*' (Holland Report, paragraph 40). On the contrary, the prevailing view of the US federal courts is that a parent corporation possesses neither legal nor equitable title in patents that are owned by its subsidiary. To the extent that Teva seeks to advance that position in the Irish Proceedings, I make the following points:*

41. *The great weight of legal authority has concluded that '*the mere fact that a corporation's subsidiary owns a patent is insufficient to establish that the corporation has equitable title to the patent.*' (*Digitech Image Techs., LLC *v.* Newegg Inc.*, 2013 WL 1871513 (C.D. Cal. 2013)). One Federal Circuit decision,* Spine Solutions, Inc. *v.* Medtronic SofamorDanek USA, Inc.*, 620 F.3d 1305 (Fed. Cir. 2010), addressed the possible ownership interests of both a parent and parallel corporation of the patent owner. In that case, Spine Solutions, Inc. (SSI) was the assignee of the '071 patent. SSI was also the child corporation of another company, Synthes, Inc. In addition, SSI had a parallel corporation, Synthes Spine, that was also owned by Synthes, Inc. After bringing a cause of action for patent infringement, SSJ sought to add Synthes, Inc. and Synthes Spine to the litigation as co-plaintiffs.*

42. *The Federal Circuit made short work of concluding that neither Synthes, Inc. nor Synthes Spine were owners of the '071 patent. With respect to the parent corporation Synthes, Inc.:*

> *'It is undisputed that SSI is the sole owner of the '071 patent. With respect to Synthes, Inc., SS/'s parent corporation, the record contains no evidence that Synthes, Inc. is an exclusive licensee of the '071 patent. In fact, the amended complaint does not even allege that Synthes, Inc. licenses the '071 patent. Given that nothing in the record indicates that Synthes, Inc. is an owner or exclusive licensee of the '071 patent, we agree with Medtronic that SSI failed to show that Synthes, Inc. had standing to bring this suit.' Id. at 1317-18.*

43. *With respect to the parallel corporation Synthes Spine, the Federal Circuit weighed the evidence before it as follows, id. at 1318 (citations omitted):*

> 'SSI acknowledges that there is no agreement, either oral or written, between SSI and Synthes Spine with respect to the '071 patent. However, SSI asserts that an 'understanding' exists within the Synthes family that Synthes Spine has the exclusive right to practice the '071 patent. SS/ points to deposition testimony from its corporate representative-Robert Donohue, the Chairman of SSI and Chief Financial Officer of Synthes, lnc.-that this 'understanding' is 'based on the fact that [Synthes Spine] has the exclusive right to market and distribute all spine-related products in the U.S.... I'm not aware of an expressed agreement that is oral or written. I believe it's an agreement between the parties based on the way Synthes is organized.''

44. *The Federal Circuit rejected the argument that an 'understanding' among distinct corporate entities somehow amounted to .a written assignment of rights, as the US patent statute requires. In reaching this conclusion, the Federal Circuit recognized that if it were to allow Synthes, Inc. and Synthes Spine to join the litigation, 'any company related to a patent owner' would be deemed to have an ownership interest in the patent, 'regardless of any actual agreement as to exclusivity.' The Federal Circuit particularly pointed out that mere evidence of the ''organization'' of three related entities did not somehow impart an ownership interest in one patent to each of them.*

45. *Another leading Federal Circuit case,* Abraxis Bioscience, Inc. *v.* Navinta LLC*, 625 F.3d 1359 (Fed. Cir. 2010), considered a complex series of transact1ons among related corporate entities. In that case, AstraZeneca ('AZ-UK') and Abraxis entered into an Asset Purchase Agreement on 26 April 2006. The agreement provided that AZ-UK 'shall cause' the transfer of three patents to Abraxis. However, at that time, those patents were owned by Astra Lakemedel Aktiebolag ('Astra L') and AstraZeneca AB ('AZ- AB'), not AZ-UK. AZ-*

UK subsequently attempted to assign the patents to Abraxis on 28 June 2006, even though it still did not own the patents. On 15 March 2007, Abraxis sued Navinta LLC for patent infringement on the three patents. On the same day, AZ-AB and Astra L assigned the patents to AZ- UK, but not to Abraxis. Subsequently, on 12 November 2007, AZ-UK finally assigned the three patents to Abraxis.

46. *On its way to concluding that Abraxis did not qualify as an owner of the three patents on the date that suit was filed, the Federal Circuit explained, Id. at 1366:*

> *'*Whether Astra L, AZ-AB, and AZ-UK are part of the same corporate structure and are not 'complete strangers,' therefore, is irrelevant because there was no valid written assignment to Abraxis. (See 35 U.S.C. § 261) (assignments of patents must be in writing) ...Common corporate structure does not overcome the requirement that even between a parent and a subsidiary, an appropriate written assignment is necessary to transfer legal title from one to the other.*'*

Although the Abraxis *v.* Navinta *opinion spoke towards legal title, its reasoning and ruling-as well as the language in the earlier Spine Solutions opinion - makes plain that Abraxis did not possess equitable title either. Otherwise this litigation could have proceeded under this alternative ground, for the only remedy sought by Abraxis was equitable relief, namely, an injunction against future infringement. (See Id. at 1361-62 (noting that the accused infringer had not yet sold or offered to sell its generic product)).*

47. *Several district courts have built upon the analysis in* Spine Solutions *and* Abraxis *v.* Navinta *in other scenarios involving members of the same corporate family. In the* Digitech *v.* Newegg *case, Digitech was the owner of legal title to the '415 Patent, and was also the wholly owned subsidiary of Acacia Research Corporation. The two corporations shared the same physical address and place of business. The District Court readily concluded that 'Acacia cannot be deemed to have equitable title to the patent merely because it owns and exercises control over its subsidiary.' Id. at *5. In reaching this conclusion, the District Court for the Central District of California recognized that the* 'Federal Circuit has never held that a corporate parent has equitable title in its subsidiary's patents.*' Id. Instead, the concept of equitable title has applied only to contractual arrangements to assign rights from an inventor to another entity.*

48. *Noting that US corporate law 'sets clear boundaries between parents and subsidiaries,' id., the court explained:*

> *'Patent rights are not acquired unless authorized by, and acquired in, the manner prescribed by statute. While Courts permit true equitable-title holders to proceed out of fairness, equitable rules were not intended to circumvent policies and rules having their source in the patent statutes. The Court cannot find that mere ownership of corporate stock can convey equitable title in a patent without contravening the clear restrictions of both corporations and patent law. Such a holding would lead to absurd results.'*

Id. at 5 (citations omitted). As a result, 'Acacia's parent-subsidiary relationship with Digitech did not convey any cognizable interest in the '415 Patent-legal or equitable.' Id.

49. *Other judicial decisions are to similar effect. For example, in* Top Victory Electronics *v.* Hitachi Ltd.*, 2010 WL 4722482 (N.D. Cal. 2010), the court rejected Hitachi's argument that it was the equitable title holder of the asserted patents that were owned by its subsidiaries HCE and HAD. Hitachi's argument was that the companies 'were closely intertwined by virtue of their parent/subsidiary relationship' failed to convince the court that Hitachi had any ownership interest in the patents whatsoever. Id. at 3-4.*

50. *Other cases reaching the same result include* Quantum Corp. *v.* Riverbed Tech., Inc.*, 2008 WL 314490 at *3 (N.D. Cal. 2008) (a company's control of its patent-holding subsidiaries does not convey standing);* DePuy, Inc. *v.* Zimmer Holdings, Inc.*, 384*

F.Supp.2d 1237 (N.D. Ill. 2005) (corporate parent of wholly owned subsidiary lacks standing to sue when the subsidiary owns the patent); Beam Laser Systems, Inc. *v.* Cox Communications, Inc.*, 117 F.Supp.2d 515, 520-21 (E.D. Va. 2000) {the sole shareholder of a patent-owning corporation does not possess equitable title of them); and* Steelcase Inc. *v.* Smart Technologies Inc.*, 336 F.Supp.2d 714, 719 (W.D. Mich. 2004) (with respect to Delaware corporations, '*a parent does not have equitable title solely by virtue of its ownership of the subsidiary.*').*

51. *I therefore respectfully disagree that BMS Company could be regarded as the beneficial owner of the earlier filed patent application, as contended in the Holland Report (at paragraph 40). The US courts have persistently rejected the argument that a corporate parent possesses either legal or equitable ownership of a patent owned by its subsidiary. As a result, BMS Pharma Company, and not BMS Company, was the owner of the inventions claimed in the US165 filing as of 3 November 2001. Further, BMS Company did not, by virtue of a purported assignment in 2007, establish itself as a successor in title to BMS Pharma Company in a timely manner.*

COMMENTS ON THE EXPERT REPORT OF DONALD S. CHISUM

52. *I have also had the opportunity to review the Chisum Report. I understand that Professor Chisum issued his statement in connection with proceedings in other European jurisdictions, and in response to the Thomas Italian Report.*

53. *I understand that the Chisum Report has not been delivered for the Irish Proceedings, but that it may be of assistance to the Irish Court for me to give my views of the issues raised and relied on by BMS Ireland and its expert witnesses in related proceedings in other jurisdictions and for this reason I address certain aspects of the Chisum Report here.*

54. *While I hold Professor Chisum in high regard as a senior member of our shared academic community, I respectfully disagree with his criticisms of the Thomas Italian Report.*

55. *The Role of Section 118 of the US Patent Act. Professor Chisum cites section 118 of the US Patent Act, as it was worded at times relevant here, as support for the 'principle that a person or entity may have equitable rights to an invention or patent right even there is no written assignment of legal title.' (Chisum Report, paragraph 10.) Section 118 was in fact a narrowly drawn provision that speaks to circumstances not relevant to the present matter. It provides in pertinent part:*

> *'Whenever an inventor refuses to execute an application for patent, or cannot be found or reached after diligent effort, a person to whom the inventor has assigned or agreed in writing to assign the invention or who otherwise shows sufficient proprietary interest in the matter justifying such action, may make application for patent on behalf of and as agent for the inventor on proof of the pertinent facts and a showing that such action is necessary to preserve the rights of the parties or to prevent irreparable damage; and the Director may grant a patent to such inventor upon such notice to him as the Director deems sufficient, and on compliance with such regulations as he prescribes.'*

56. *This statute thus made clear that if an inventor is either uncooperative or unavailable, the holder of equitable title in the relevant invention may prosecute a patent application in the US. My understanding is that neither of those circumstances apply here. And by its own terms, section 118 did not permit the prosecution of patent applications by purported equitable title holders in other circumstances-and in particular, where equitable title is claimed by a related corporate entity owns title to the invention.*

57. *As Professor Chisum noted in paragraph 10 of his opinion, the US Congress subsequently amended section 118 in order to allow anyone who 'otherwise shows sufficient proprietary interest in the matter' to also file for a patent. Perhaps this more comprehensive category could potentially include members of the same corporate family in appropriate circumstances, but that matter is not before this Court. In my professional opinion,*

however, US courts would not apply this more permissive filing standard to applications under the previous version of section 118.

58. *The Role of Standing. In the Chisum Report, Professor Chisum summarily dismisses the long list of US judicial opinions holding that corporate parents do not hold equitable title in patents owned by their subsidiaries. In his opinion, because these rulings arose in cases that primarily pertained to standing, they are simply irrelevant to ownership. I respectfully disagree with this conclusion. Simply because a principle of law is frequently articulated within one context does not suggest that it does not apply equally in a related context.*

59. *This view also misapprehends the notion of standing. Whether an entity possesses standing to sue for patent infringement comprises a multi-component inquiry that ultimately requires a dispute that is 'definite and concrete, touching the relations of parties having adverse legal interests.'* MedImmune, Inc. *v.* Genentech, Inc.*, 549 U.S. 118, 127 (2007) (citation omitted). The dispute must also be '*real and substantial*' and '*admi*[t]* of legal relief through a decree of conclusive character, as distinguished from an opinion advising what the Jaw would be upon a hypothetical state of facts.' Id. An assessment of ownership forms one component of determining standing to sue for patent infringement, but it is one of several. Ownership is not the same as standing, and thus the standing cases discussing ownership cannot be dismissed because they supposedly deal with an unrelated issue.*

60. *Professor Chisum also asserts, in paragraph 16 of the Chisum Report, that section 261 of the US Patent Act is limited to determining whether a "patentee" has standing to sue for patent infringement. To the contrary, section 261 expressly refers to patent applicants. I further observe that a 'patentee' is simply a successful patent applicant, namely the inventor or the inventors, or alternately an assignee. The distinction drawn here is one without a dlfference. As Professor Chisum explains in his treatise, 8 CHISUM ON PATENTS§ 22.01 (2022):*

> *'The presumptive owner of the property right in a patentable invention is the single human inventor, in the case of a sole invention, or the several human inventors, in the case of a joint invention. The inventor or inventors may then transfer ownership interests by written assignment to anyone (including a corporation or other entity) and may in fact be under a legal duty to do so by virtue of a contractual or other obligation, as in the case of an employee who has signed a contract requiring that he/she assign inventions made during the course of employment.N [I assume the 'N' should be a single apostrophe].*

61. *I additionally note that US courts respect the formal differences between members of the same corporate family across the gamut of patent law issues. With respect to remedies, for example, sometimes one corporate entity owns patents while a related company manufactures and sells the patented products. If the patent owner prevails in an infringement suit against a competitor under these circumstances, US courts ordinarily refuse to award damages based on lost profits-after all, the patent owner itself made no profits from the patents to begin with. A reasonable royalty should be awarded instead. Arguments that lost profits should be available across various corporate organizational constructs are ordinarily to no avail. See* Mars, Inc. *v.* Coin Acceptors, Inc.*, 527 F.3d 1359, 1367 (Fed. Cir. 2008) (declining to award damages to a patent holding corporation due to the lost profits of its wholly owned subsidiary). See also* Poly-America, L.P. *v.* GSE Lining Technology, Inc.*, 383 F.3d 1303, 1311 (Fed. Cir. 2004) (separate members of a corporate family '*may not enjoy the advantages of their separate corporate structure and, at the same time, avoid the consequential limitations of that structure ...*').*

62. *Another topic where distinctions among related corporate entities matter include that of enforceability. In* Email Link Corp. *v.* Treasure Island, LLC*, 2012 WL 4482576 (D. Nev. 25 Sept. 2012), two patents with substantially similar claims were held by two companies with a common corporate owner. One of the patents, issued later than the other, was subject to a terminal disclaimer under the doctrine of double patenting. The District Court held that the*

later-issued patent was unenforceable because the two firms were distinct enterprises, despite having the same corporate parent. In reaching this result, the District Court cited* United States *v.* Bennet*, 621 F.3d 1131, 1136 (9th Cir. 2010), for the proposition that '[t]*oday, it almost goes without saying that a parent corporation does not own the assets of its wholly- owned subsidiary by virtue of that relationship alone.*' Id. at "4.*

63. *Yet another area showing the same respect for corporate boundaries is liability for patent infringement. As the Delaware federal district court confirmed recently, absent a special showing, parent corporations are not liable for infringements committed by their subsidiaries. See* M2M Solutions LLC *v.* Te/it Communications *PC, 2015 WL 4640400 at *3 (D. Del. 2015).*

64. *Although I will refrain from stepping through the entire range of patent law subjects for which corporate structure is relevant, I will provide my professional opinion that US courts respect the enterprise organization that patent holders-or their related entities-have themselves established. This uniform approach makes sense as a matter of innovation policy, for it makes little sense to have ownership of a particular invention, patent application, or patent depend upon which doctrine is being applied. To put the matter squarely, in the US at least, one person cannot be the owner of an invention, patent application, or patent with respect to one legal issue, while a different person owns it for another.*

65. *Other Cases Cited by Professor Chisum. In paragraph 4 of the Chisum Report, Professor Chisum cites* Schwendimann *v.* Arkwright Coating*, 959 F.3d 1065 (Fed. Cir. 2020).* Schwendimann *was a case involving standing to sue for infringement, and to the extent that Professor Chisum recognizes that this line of cases is highly pertinent to the present matter, I agree with him. I further observe that* Schwendimann *involved the interpretation of a written agreement transferring title to patent rights, and I also agree that a written instrument is required to assign patent rights under section 261 of the US Patent Act.*

66. *Professor Chisum cites* Dalzell *v.* Dueber Watch-Case Manufacturing Co.*, 149 U.S. 315 (1893), in paragraph 6 of the Chisum Report. The* Dalzell *decision involved a former employer's attempt to compel a former employee to assign patent rights based upon inventions ostensibly made during the course of employment, as well as alleged affirmative representatives that he would so assign the patent rights. In my professional opinion, this nineteenth century opinion, involving entirely dissimilar facts to the present matter, has nothing to teach us about the relevance of Delaware corporate law to the facts at hand.*

67. *Finally, in paragraph 22, Professor Chisum voices his opinion that* Abraxis Bioscience, Inc. *v.* Navinta *LLC, 625 F.3d 1359 (Fed. Cir. 201O} is not a leading case. Although whether a particular judicial opinion qualifies as a 'leading case' may be a subjective determination, according to the Westlaw database, the decision has been cited 975 times by different sources.*

68. *Evidence of an Assignment. Paragraph 17 of the Chisum Report asserts what appears to be an alternative argument to the one based upon a construct of Delaware corporations. There, he questions whether an email chain provided a written assignment sufficient to provide BMS Company with equitable title in the patents owned by BMS Pharma Company.*

69. *I agree with Professor Chisum that, as a general matter, an email chain could constitute an instrument in writing. However, I have reviewed the Golian Witness Statement. That Statement largely describes emails sent prior to Mr Golian's employment by BMS Company. None of these emails includes any language whatsoever that could be described as conveying intellectual property from one entity to another. Rather, Mr Golian and the other individuals described in the Golian Witness Statement appeared to operate under the assumption that title would be transferred merely by changing the name of the firm from DuPont Pharmaceuticals Company to BMS Pharma Company. I am unaware of any case or other competent legal authority in the US holding that a change in an enterprise's trade name somehow transfers title of property owned by that enterprise to another.*

ADDITIONAL REMARKS

70. *I wish to make two additional observations.*

71. First, I am under the impression that the corporate organizational chart presented in the Holland Report provides a severely truncated account of the vast, global network of BMS corporations and other enterprises. As a result, BMS is essentially arguing that it possesses a patent interest in any one of the inventions owned by any of its subsidiaries anywhere in the world-likely comprising many dozens or hundreds of enterprises. Going forward, I see no further reason why the argument of BMS Ireland could not be extended to assert that any subsidiary owned by BMS Ireland possesses equitable title in inventions by any other member of its corporate family. This position would establish a very large number of potential owners of any BMS patent Either of these situations would conflict with the policy goals of making ownership of patent rights orderly and predictable.

72. Second, insofar as Teva seeks to rely on a view (as expressed by the late Justice Holland) that ownership issues pertaining to patents are merely technical, I respectfully disagree with that suggestion as a matter of Innovation policy. When a patent is infringed, the damage from that infringement may redound to many others besides the patent proprietor. Corporate entities that are related to the patentee, including suppliers, distributors and retailers, may suffer reduced sales or other financial harms. Yet none of those losses would be protected by the law if these related entities did not own the patent Knowing which enterprise actually possesses title to an invention prevents uncertainty and expansion of the patent right, and also allows the USPTO to set clear boundaries on who may acquire and assert a patent, and what potential harms that enterprise may suffer if the patent is infringed.

CONCLUSION

73. Section 261 requires a written agreement for applications for patent, patents, or any interest therein to be assigned from one entity to another. While the term "writing" is construed broadly, that writing must contain words of conveyance sufficient to transfer ownership. For the most part, state contract law governs the ownership issues resulting from assignments, in the sense that principles ofstate law are used to determine whether a contract has been formed, how the contractual language should be interpreted, whether the contract has been breached, and related issues. In the absence of a written assignment, US courts have refused to allow companies related to the patent owner to claim either a legal or equitable interest in that patent because the companies are commonly owned.

Statement #2 of 2

INTRODUCTION

1. I am the same John R. Thomas who previously submitted an expert report on 14 April 2022 in these proceedings.

2. I have been provided with, and had the opportunity to review, the Statement of Professor Donald Chisum dated 13 May 2022 (the "Chisum Statement"). My review of the Chisum Statement confirms my earlier opinion that under US federal law, corporate parents do not possess equitable title to patents owned by their subsidiaries merely by reason of the corporate relationship.

GENERAL OBSERVATIONS

3. In general, although Professor Chisum asserts that judicial opinions pertaining to standing are irrelevant to the determination of equitable title in this matter, he continues to cite them in support of his contentions. See, e.g., Schwendimann v. Arkwright Advanced Coating, Inc., 959 F.3d 1065 (Fed. Cir. 2020) (Chisum Statement at paragraph 16); Arachnid, Inc. v. Merit Industries, Inc., 939 F.2d 1574 (Fed. Cir. 1991) (Chisum Statement at paragraph 21); Steelcase Inc. v. Smart Technologies Inc., 336 F.Supp.2d 714 (W.D. Mich. 2004) (Chisum Statement at paragraph 46). In contrast, Professor Chisum does not cite a single source

stating that equitable title determinations with respect to standing are limited to that context, or that the definition of equitable title differs elsewhere. As a result, I once again agree with Professor Chisum that the US judicial opinions discussing equitable title, whether in the context of standing or another issue, are highly probative and indeed dispositive of the issue of international priority presented in these proceedings.

4. *Also, as a general matter, Professor Chisum provides succinct quotations from judicial opinions regarding the application of state law to ownership issues without explaining the context in which they arose. In doing so, Professor Chisum fails to acknowledge that the recognition of equitable title has been limited to circumstances where an assignment of patent rights affirmatively occurred. See, e.g., Digitech Image Techs., LLC v. Newegg Inc., 2013 WL 1871513, at *4 n.3 (C.D. Cal. 2013) ('The only Federal Circuit cases that recognize an equitable title to a patent involve contractual arrangements to assign rights in inventions between the asserted equitable-title holder and the inventor. The Federal Circuit has also alluded to equitable title where the rights to a patent are being held in a trust.'); Beam Laser Sys., Inc. v. Cox Communications, Inc., 117 F.Supp.2d 515, 520 n.6 (E.D. Va. 2000) ('The only cases from the Federal Circuit recognizing an equitable title to a patent, of which the court is aware, involve a contractual arrangement between the party claiming to hold equitable title and the inventor, pursuant to which the inventor assigned his rights in any invention prior to the existence of an invention, and the assignee later—i.e., after the invention came into being—claimed to have equitable title to the invention.'). I observe that Professor Chisum cites Beam Laser and the quotation above, in Sections 21.02 and 21.03 of Chisum on Patents.*

5. *The decision of Chief Judge F. Dennis Saylor IV of the US District Court of Massachusetts in Maquet Cardiovascular LLC v. Abiomed R&D, Inc., 2018 WL 4211364 at *4 (D. Mass. 2018) is instructive on this point. He there explained that the 'Federal Circuit has recognized that a party may hold equitable title to a patent without holding legal title to it, either because the party with legal title only acquired it by breaching a contract with the equitable title holder or because the party with legal title improperly failed to name the equitable title holders as inventors.' Maquet Cardiovascular LLC v. Abiomed R&D, Inc., 2018 WL 4211364 at *4 (D. Mass. 2018). Chief Judge Saylor further reasoned, id.:*

> *'The Court is wary of extending the doctrine of equitable title to situations where a corporate parent exercises control over a patentee-subsidiary. Generally, remedies in equity are created in order to avoid unfair results. There is nothing unfair about a corporate subsidiary owning title to a patent, or a corporate parent exercising substantial control over its subsidiary. Furthermore, it is not clear how far such an equitable right would extend and how it would be exercised—surely not every corporate parent has an equitable title to patents held by every corporate subsidiary. Perhaps most importantly, extending the doctrine in such circumstances directly contradicts the statutory requirement that assignment of patent rights must be by an 'instrument in writing.' See 35 U.S.C. § 261.*

6. *In particular, every judicial opinion that Professor Chisum independently identified involved an actual and affirmative transfer of patent rights from one entity to another. These opinions include:*

a. Schwendimann *v.* Arkwright Advanced Coating, Inc.*, 959 F.3d 1065, 1069 (Fed. Cir. 2020) (Chisum Statement at paragraph 16) concerned a written assignment.*

b. Dalzell *v.* Dueber Watch-Case Mfg. Co.*, 149 U.S. 315, 320 (1895) (Chisum Statement at paragraphs 19, 24) involved an '*oral agreement for the sale and assignment*'of patent rights.*

c. Dickman *v. Vollmer, 303 Wis. 241, 244 (Wis. Ct. App. 2007) (Chisum Statement at paragraph 23) explained '*that the parties orally agreed to assign the patent.*'*

d. SourceProse Corp. *v.* RPX Corp.*, 2017 WL 373065, at *1 (N.D. Cal. 2017) (Chisum Statement at 24) pertained to '*an oral agreement for the sales of patents.*'*

e. Board of Trustees of the Leland Stanford Junior University *v.* Roche Molecular Sys.*, 563 U.S. 776 (2011) involved an inventor who executed written assignment agreements with*

two different enterprises.

f. Arachnid, Inc. *v.* Merit Industries, Inc.*, 939 F.2d 1574, 1576 (Fed. Cir. 1991) (Chisum Statement at paragraph 39) addressed a written assignment.*

7. *None of these decisions supports the contention that related corporate entities somehow passively possess an ownership interest in each other's patents.*

SPECIFIC OBSERVATIONS

8. *In paragraph 14 of his Statement, Professor Chisum states that I have not previously cited any judicial opinion that rejected, based on federal law, any state-based ownership of patent rights. I will do so now, noting that some of the following cases are themselves cited in Chisum on Patents. One such case is* Ager *v.* Murray*, 105 U.S. 126 (1891*)[sic -1881?], *a US Supreme Court decision of even older vintage than Dalzell, that Professor Chisum identifies in Section 9300 of his treatise. There, the Court affirmed the ruling of the Supreme Court of the District of Columbia that a judgment creditor could not seize a debtor's federally granted patent through resort to state law. The Court explained that '[t]*here is nothing in any act of Congress, or in the nature of the rights themselves, to give them locality anywhere, so as to subject them to the process of courts having jurisdiction limited by the lines of States and districts.*' Id. at 130 (citing* Stevens *v.* Gladding*, 58 U.S. 447 (1854)). Although the Court suggested that the state court might be able to compel a written assignment to the debtor, consistent with federal law now housed in Section 261 of the Patent Act, the Court concluded that state law could not be used to transfer ownership of patent rights to settle a money judgment. See also* McClaskey *v.* Harbison-Walker Refractories Co.*, 138 F.2d 493 (3d Cir. 1943) (assessing whether a sheriff's sale of a patent seized under Pennsylvania law complied with R.S. 4898, the predecessor of Section 261).*

9. *Another issue where federal law dominates is the determination of inventorship. '*The federal Patent Act leaves no room for states to supplement the national standard for inventorship.*'* University of Colorado Foundation, Inc. *v.* American Cyanamid Co.*, 196 F.3d 1366, 1372 (Fed. Cir. 1999). And under US law, the inventors are deemed the initial owners of an invention, patent application, or patent. See* Beech Aircraft Corp. *v.* EDO Corp.*, 990 F.2d 1237, 1248 (Fed. Cir. 1993) ('*At the heart of any ownership analysis lies the question of who first invented the subject matter at issue, because the patent right initially vests in the inventor who may then, barring any restrictions to the contrary, transfer that right to another, and so forth.*'). See also* In re CFLC, Inc.*, 89 F.3d 673, 679 (9th Cir. 1996) ('*[F]ederal law governs the assignability of patent licenses because of the conflict between federal patent policy and state laws, such as California's, that would allow assignability.*'); *FASA Corp. *v.* Playmates Toys, Inc.*, 892 F. Supp. 1061, 1064, 1068 (N.D. Ill. 1995) (ruling that federal law deems unenforceable a contractual covenant requiring '*an inventor to waive all rights to the invention" due to the "public policies underlying the . . . patent laws.*').*

10. *In paragraph 15 of the Chisum Statement, Professor Chisum states that I '*postulate that there is, or should be, for 'policy' reasons, a 'uniform' approach to 'corporate structure' . . . .*' While I certainly believe that innovation policy supports current US law as I have presented it to this court, I have not relied merely upon policy arguments. To the contrary, I have cited numerous judicial opinions and other authorities that consistently refuse to recognize equitable title in circumstances analogous to this case. By contrast, Professor Chisum has not cited even a single reference–not one authoritative source, commentator, or even his own treatise—that propounds a contrary position.*

11. *Professor Chisum takes great stock in the venerable* Dalzell *case, but like the other judicial opinions he cites,* Dalzell *involved an affirmative act that transferred ownership—namely a putative oral assignment by an employee who was hired to invent. As a result, I continue to believe that Dalzell lacks pertinence to the current matter. Nonetheless, Professor Chisum asserts in paragraph 20 of his Statement that '[c]*onsistent with Dalzell, Section 261 has never been applied in a case involving a dispute over ownership of a patent priority right (as opposed to ownership for purposes of standing to sue for infringement of a patent).*' He repeats this assertion in paragraph 31 of his Statement. These opinions are plainly incorrect, as indicated by a judicial opinion that Professor Chisum cited with approval in*

his treatise.

12. *In* Hewett *v.* Samonsite Corp.*, 507 P.2d 1119 (Colo. App. 1973), the Colorado Court of Appeals (a state court of second instance) applied Section 261 immediately after recognizing the impact of Dalzell. There, Hewett had been employed by Samsonite in a non-inventive capacity. Hewett nonetheless developed several inventions that were later patented. At issue was whether several releases signed by Hewett conveyed ownership of the patents to Samsonite. The Court of Appeals concluded, id. at 1122:*

> *As stated in Dalzell v. Dueber Watch Case Manufacturing Co., Supra, an employer is not entitled to a conveyance of patents obtained for inventions made by an employee in the absence of an express agreement.*

35 U.S.C. §261 provides that patent applications, patents, or any interest therein are assignable 'by an instrument in writing.' Patents and rights in patents are incorporeal personal property. Patterson v. Kentucky, 97 U.S. 501, 24 L.Ed. 1115. An instrument which is claimed to be an assignment of a patent right must adequately express an intention to transfer ownership of the patent right. United States v. Krasnov, D.C., 143 F.Supp. 184. Therefore, the releases did not affect any change in the ownership right between the parties. Hewett still retains his original interests in the inventions and subsequent patents, and Samsonite continues to hold its shop rights thereto.

13. Hewett *v.* Samonsite Corp. *had nothing to do with standing. Rather, the parties disputed the ownership of Hewett's inventions and the patents covering those inventions. And in this context, after recognizing Dalzell and applying Section 261, the state court held that any instrument asserting to assign patents must do so with clarity.*

14. *Professor Chisum referenced* Hewett *v* Samsonite Corp. *with approval in section 22.03 of Chisum on Patents. I agree with him that* Hewett *v.* Samsonite Corp. *correctly reflects US law, particularly as it applies Section 261 to an ownership dispute without regard to the law of standing; and also in its insistence that the ownership of patent rights must be expressly transferred in an unambiguous manner. Amongst other state court decisions, Bennett v. American Electric Power Service Corp., 2001 WL 1136150 at *4 (Ohio App. 2001) is to similar effect.*

15. *Numerous opinions from the federal courts have also applied Section 261 in cases addressing the ownership of patents even though standing is not at issue. See, e.g., C.R. Bard, Inc. v. Medical Components, Inc., 2021 WL 2873802, at *2 (D. Utah 2021) (addressing ownership and citing Section 261 for the proposition that a patent assignment must be in writing); Yufa v. TSI Inc., 2018 WL 3956489, at *5-6 (N.D. Cal. 2018) (interpreting Section 261 with respect to a receivership); S3 Graphics Co. v. ATI Techs., ULC, 2015 WL 7307241, at *9 (D.Del. 2015) (analyzing assignments for compliance with Section 261); McClaskey v. Harbison-Walker Refractories Co., supra. These and other judicial opinions reveal that Section 261 is hardly limited to matters of standing. Rather, Section 261 speaks broadly towards the controlling requirements to transfer title.*

16. *Paragraph 26 of the Chisum Statement states that 'Section 118, in both its earlier and later form, represent a recognition in the federal patent statutes of the established general principle that there can be a 'proprietary' interest, i.e., ownership, in an invention and patent priority rights beyond those already perfected by a written assignment complying with the federal statutes (i.e., Section 261).' I agree with Professor Chisum that Section 118 identified circumstances where one other than the inventor may file a patent application at the USPTO. However, I disagree with his view that Section 118, as it was then framed, afforded an expansive ability for individuals and enterprises to assert equitable ownership and hence file patent applications at the USPTO. Section 118 on its face applied only when inventors were absent or recalcitrant. Professor Chisum's problematic view would render the relevant, predecessor version of Section 118 superfluous, and further suggests that the US Congress need not have bothered to amend that statue in 2011 to permit assignee filing at the USPTO.*

17. *In paragraph 27 of his Statement, Professor Chisum says that I have incorrectly stated that* 'federal law governs the way in which an assignment of patent rights (including the right to

claim priority) can be made.*' This account should be contrasted with the statement in Section 22.01 of the Chisum on Patents treatise that the federal* 'patent statutes . . . provide that both patents and patent applications shall be 'assignable in law by an instrument in writing.'*' Likewise, in* Site Microsurgical Systems Inc. *v.* Cooper Companies Inc.*, 797 F.Supp. 333, 335 n.2 (D.Del. 1992), the federal court explained (with emphasis added):*

> *The patent laws specifically provide for the transfer of rights. 35 U.S.C. § 261. Patent rights can be transferred either by assignment or by license. An assignment will be deemed to be a matter of federal patent law whereas a license will normally be governed by state- based contract law. A patent owner can either assign his/her entire interest or assign an undivided portion, making the patentee and the assignees joint owners of the whole interest secured by the patent.*

18. *The Delaware federal court then cited to D. Chisum, Patents: A Treatise on the Law of Patentability, Validity and Infringement § 21.03[2][a] (MB 1991). In Section 22.01 of his treatise, in footnote 3, Professor Chisum references Site Microsurgical with approval, reprints the text quoted above, and further indicates that his treatise was cited in that opinion. In my professional opinion, the position taken in Site Microsurgical and in Chisum on Patents accurately reflects US law.*

19. *In paragraph 46 of his Statement, Professor Chisum considers Steelcase, Inc. v. Smart Technologies, Inc., 336 F.Supp.2d 714 (W.D. Mich. 2004) and Beam Laser Systems, Inc. v. Cox Communications, Inc., 117 F.Supp.2d 515 (E.D. Va. 2000). According to Professor Chisum, in Steelcase 'the district court carefully considered the facts and found standing for one subsidiary but not the other.' In fact, the Steelcase court held that the patentee's corporate parent possessed sufficient rights in the asserted patent because it was a sole licensee, had been affirmatively granted exclusive rights to practice the patented invention, and had been affirmatively granted the right to enforce the patent. Id. at 718. Importantly for this matter, the Steelcase court expressly rejected the notion that common corporate ownership, absent this sort of affirmative transfer, sufficed to grant equitable title in another enterprise's patent. Id. at 718-19.*

20. *In the same paragraph of his Statement, Professor Chisum encounters difficulties with the holding of Beam Laser and is left to assert that the case was wrongly decided. (Chisum Statement at paragraph 46). According to Professor Chisum, had Chief Judge Rebecca Beach Smith followed the line of reasoning that he now advocates, then she would have reached a different outcome. I disagree, as Chief Judge Smith's conclusion that '[o]wnership of corporate stock does not create equitable title in that corporation's property' correctly states US law. As I noted earlier, Beam Laser has been cited with approval in two different sections of Chisum on Patents.*

21. *Professor Chisum and I agree, as he states in Paragraph 47 of his Statement, that accused infringers often contest standing because it serves as a predicate for maintaining a patent enforcement lawsuit in federal court. However, he objects to my assertion that '[s]imply because a principle of law is frequently articulated within one context does not suggest that it does not apply equally in a related context." Although Professor Chisum observes that I did not cite any authority for this axiomatic principle, he cites none for his contrary view.*

22. *The proposition that property rights should be orderly and predictable cannot be gainsaid. Nonetheless Professor Chisum seemingly disagrees with it in paragraph 55. In this respect, his opinion conflicts with that of the US Congress and courts, which have repeatedly emphasized that patents should provide public notice of what subject matter is proprietary, who owns the patent, and what the consequences of infringement would be. See, e.g., Nautilus, Inc. v. Biosig Instruments Inc., 572 U.S. 898 (2014); Festo Corp. v. Shoketsu Kinzoku Kabushiki Co., 535 U.S. 722 (2002); Warner- Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17 (1997). I also wish to direct attention to a recent hearing of the Judiciary Committee of the US Congress pertaining to patent ownership. US Congress, Committee Hearing, Pride in Patent Ownership: The Value of Knowing Who Owns a Patent (19 Oct. 2021) (hearing of the US Senate Committee on the Judiciary, Subcommittee on Intellectual*

Property) (available at www.judiciary.senate.gov). Participants in this hearing explained the current US law of patent ownership, what steps the USPTO takes to promote clarity of patent ownership, and the significant ramifications that result based upon the use of a patent by a specific patent owner. That the US Senate would recently conduct a public hearing on patent ownership further evidences the fact that it is not merely a technical or trivial matter under US law.

23. *In paragraph 56 of his Statement, Professor Chisum asserts that the USPTO 'does not resolve disputes about ownership' and cites to his treatise. This statement is plainly incorrect, as any reader of Chisum on Patents would discern. As Professor Chisum explains in the very section that he cites, Section 11.20[2][a][ii):*

> *[R]ecognition of an assignee's right to prosecute forces [USPTOJ [sic] to resolve some disputes between inventors and parlies who claim to be assignees. Problems have arisen during prosecution of assigned applications when an assignor-inventor did not approve of an assignee's actions or there are joint inventors and separate assignees.*

CONCLUSION

24. *Two consistently stated principles of US law are worth noting for purposes of this litigation.*
a. One is that 'more than a century of corporate law' in the United States holds that a parent corporation does not own the assets of its subsidiaries. United States *v.* Bennett, *621 F.3d 1131, 1136 (9th Cir. 2010) (further observing that in '1959, the Delaware Supreme Court rejected an argument-much like that presented here-that a parent corporation owns its wholly-owned subsidiary's assets. See* Buechner *v.* Farbenfabriken Bayer*, 154 A.2d 684, 686 (Del.1959).').*
b. The other is that the US Supreme Court has repeatedly decried the creation of special rules, outside the mainstream of US law and equitable practice, for patent cases. See, e.g., eBay Inc. *v.* MercExchange, LLC*, 547 U.S. 388 (2006) (overturning lower court decisions that departed from mainstream equitable principles).*
c. Professor Chisum views the priority issue before this court as a knotty one, but in truth it is straightforward. The case law ruling that corporate parents do not possess equitable title in patents owned by their subsidiaries is overwhelming. Many dozens of US judicial opinions reject this theory of ownership, and Professor Chisum does not cite a single source that says otherwise. As a result, this court has no reason to proceed to Delaware because the case law I have cited is dispositive of the matter."

APPENDIX 15

Abridged Written Evidence of Dr Wargin

Statement #1 of 2

"[1]...*Skilled Person/ Skilled Team*

4.1 *The concept of the 'skilled person or team' has been explained to me as a hypothetical construct which has been developed to help the court read and understand patents essentially from the point of view of a person with an interest in reading the patent at the time it was written. My understanding of the concept of the skilled person, or by extension the skilled team, as explained to me is that the individual is a person skilled in the art to whom a patent is addressed and who would have a practical interest in the subject matter of the patent. The skilled person (which can be a skilled team) is uninventive but has the common general knowledge in the relevant field (common general knowledge is addressed at paragraph 5 below).*

4.2 *I also understand that the relevant time for consideration is the Relevant Date. By 2001 I had over 20 years experience in the area of pharmacokinetics with 18 of those years within the pharmaceutical industry.*

4.3 *Having reviewed WO652 with a view to considering who should be regarded as the skilled person / skilled team I am satisfied that it is primarily addressed to a skilled team comprising a pharmacologist and a medicinal chemist. While a pharmacokineticist would be involved in drug discovery and development in 2001, I am not of the view that WO652 is addressed to, or of any interest to a skilled pharmacokineticist as there is a lack of explicit pharmacokinetic information in WO652.*

4.4 *In 2001 the skilled pharmacokineticist working on a drug discovery team would be working in collaboration with other scientists on the team, including for example biologists, pharmacologists and medicinal chemists. The skilled pharmacokineticist would be involved in evaluating compounds identified as promising by the skilled medicinal chemist and the skilled pharmacologist. The skilled pharmacokineticist would consider the physicochemical properties of such compounds and perform in vitro studies (e.g. studies to see how quickly a compound is metabolised by certain liver enzymes).*

4.5 *The skilled pharmacokineticist would also be involved in nonclinical pharmacokinetic and toxicology ("TK") study design and data analysis to provide expertise in the conduct and reporting on non-GLP and GLP studies in two species (rodent and non-rodent) required by most regulatory agencies in 2001. The information obtained in these studies would not only support the safety of the drug candidate but the pharmacokineticist would also use it to predict concentration-time data based on modelling (e.g. allometric scaling) and simulations using derived pharmacokinetics or TK parameters. The results could also be used to develop dosing regimens and pharmacodynamic ("PD") models to predict effective drug concentrations.*

4.6 *During this time the pharmacokineticist may also be working with a pharmacologist to attempt to establish a relationship between the pharmacokinetic profile and the PD profile in an attempt to develop a pharmacokinetic/PD model.*

4.7 *Based upon a consideration of the detailed responsibilities of the skilled pharmacokineticist in the various stages of drug development in 2001, WO652 contains too little relevant information/data with sufficient detail to permit the skilled pharmacokineticist with common general knowledge at the Relevant Date to conduct the necessary work.*

[2]...*Common General Knowledge*

5.1 My understanding of the concept of common general knowledge ('CGK') as explained to me is that it represents the information that is generally known to most people working in a particular field and which is generally accepted by such people as a reliable basis for further work. It encompasses information in textbooks or published review articles, which were widely read or consulted at the relevant time. It also includes material that the skilled person can call to mind or knows to exist and would refer to as a matter of course, but is not limited to the material that the skilled person has memorised. In terms of drug development, for example, the information would be that which is generally accepted by the bulk of people as a reliable basis for determining if a project should or should not continue to move forward through the stages of drug development.

5.2 I was first asked to consider CGK relevant to the skilled pharmacokineticist in 2001. The following are key CGK principles of pharmacokinetics which would have been known in 2001.

5.3 The transformation of a chemical entity into a medicine involves several well-defined steps that are driven by both science and government regulations. In the first stage, molecular entities are synthesized and tested by in vitro methods for both activity against a biological target and by various tests that predict whether the safety profile and physicochemical properties are acceptable. This is followed by tests in animals that provide additional confidence in the safety profile and potential for effectiveness. These studies include measurement of the drug in biological fluids to obtain information about how the body handles the drug, e.g. the pharmacokinetics. Next, the drug is administered for the first time in humans (usually healthy subjects) and if this is successful larger studies for efficacy are conducted. In parallel to the efficacy studies, there are often several other studies that provide useful information with respect to bioavailability and drug-drug interactions. This package of studies is submitted to regulatory bodies for consideration for approval to market the drug.

5.4 The key properties which the skilled pharmacokineticist would be interested in can be defined by four letters: ADME; absorption, distribution, metabolism and excretion. I have described these properties in more detail below. The skilled pharmacokineticist with CGK working in drug development in 2001 would be familiar with the following:

5.5 Absorption

5.5.1 The process of absorption describes how the drug enters the body following administration of the drug formulation.

5.5.2 Absorption is the process whereby a drug disintegrates, dissolves, and once in solution, permeates gastrointestinal membranes, for example, moving from the intestine into the veins surrounding the intestine to appear in the systemic circulation (e.g., blood compartment). Absorption is the first step in the process of drug delivery to the site of action in the body. In order to have a therapeutic effect a drug must reach its site of action.

5.5.3 If a drug is not absorbed but passes through the gastrointestinal tract without being absorbed it is unlikely that a disease will be cured.

5.6 Distribution

5.6.1 Following the absorption of the drug, it is necessary for an adequate concentration to move through the bloodstream to reach the site of action. For example, if a drug is intended to treat a bacterial infection, it must reach the infected site in a sufficient concentration to kill the bacteria. The processes of distribution through cell membranes into affected tissues provide the necessary concentrations.

5.6.2 Distribution is a reversible process where drugs partition into tissues and bind to plasma proteins. The process is reversible, since in most cases, the drug moves back into the systemic circulation where it can be eliminated. The amount of distribution depends on solubility and other factors that determine the movement into tissues. There are also transporters (proteins bound to membranes) that are involved in distribution processes.

5.7 Metabolism

5.7.1 After the drug is absorbed into the blood stream, the human body will often view it as a foreign substance and will try to remove it. There are processes of elimination that have evolved to convert drugs into less substances, that are 'less foreign' and can be removed.

5.7.2 Metabolism is the processes where drugs are subject to numerous enzymes in various tissues (mainly liver) or in blood whereby drugs are broken down into metabolites that are typically more polar and more readily eliminated. However, there are instances where metabolites may be as, or more, active than the parent drug.

5.8 Excretion

5.8.1 Once the body has identified a drug as a foreign substance, it will not only try to convert it to a less foreign substance, but will also try to get rid of it using the organs of excretion that it uses to rid itself of natural substances. These typically include the organs of excretion; the liver and the kidneys.

5.8.2 Excretion encompasses the major routes; renal and hepatic (e.g. biliary) as well as the minor routes; lung, skin, and others. These processes may not eliminate drugs completely with entero-hepatic recycling being a prime example.

5.9 There are several desirable properties that drugs should possess to become safe and effective medicines. These include: high bioavailability (e.g. >70%); low inter-and intra-subject variability in plasma concentrations; a sufficiently long half-life to permit a convenient dosing interval (e.g., once daily); knowledge of clearance processes; and low probability of drug-drug interactions. I have described these concepts in further detail below.

5.10 Bioavailability

5.10.1 Bioavailability is a measure of the fraction of the administered dose of a drug that is absorbed following a non-parenteral route of administration. The fraction bioavailable can range from 0 to 1/0 and is often expressed as a percentage (0 to 100%). If a drug is poorly absorbed from the gastrointestinal tract (e.g., low bioavailability) there may be insufficient concentrations to adequately treat a disease.

5.11 Inter-and intra-subject variability in plasma concentrations

5.11.1 Patients who are treated for disease by drugs vary widely due to differences in body weight and composition, genetic differences in metabolism, age effects on liver and kidney function, and many other factors. All of these factors have an effect on the way that a given individual handles a drug. As a result of these differences there may be large variability. Understanding the sources of the variability help drug developers optimize dosing regimens to provide physicians the ability to individualize those regimens.

5.12 Half-life

5.12.1 A pharmacokinetic parameter whereby the concentration of a drug decreases by one-half over 1 half-life. This value is used to design dosing regimens since a rule of thumb is to 'dose at the half-life'.

5.13 Clearance processes

5.13.1 Clearance processes include any mechanism that the body uses to rid itself of a drug or other substance. Organs such as the liver and kidneys are most important but other clearance routes such as lungs and skin can remove drugs. The relative contributions of organs to total clearance is important for understanding how disease states can impact drug disposition.

5.14 Drug-drug interactions

5.14.1 Many patients in need of drug therapy can take more than one drug to treat their disease(s). As a result it is important to understand how the presence of each can impact the concentrations of each drug. Many drugs have competing pathways of elimination and so an important topic in drug development is to understand how the interactions occur and how they can be prevented or minimized.

[3]*...WO 00/39131*

6.1 I was asked by Pinsent Masons (Ireland) to review WO131 and consider what it teaches the skilled pharmacokineticist.

6.2 First, I have set out below my analysis of WO131.

6.2.1 The majority of the first 59 pages consists of the 'Preferred Embodiments' of heterobicycle compounds with literally hundreds of functional group substitutions. This content would not be of interest to the skilled pharmacokineticist.

6.2.2 The section in WO131 that addresses the issue of a 'pharmaceutically acceptable' compound or dosage forms begins at the bottom of page 60. This section is intended to focus on potential drugs that are suitable for 'use in contact with the tissues of human beings and animals'. There is a puzzling focus on topical administration. This is apparent as the terms 'irritation' and 'allergic response' are used. The skilled pharmacokineticist would recognize that it is very unlikely that topical administration would be acceptable for inhibition of Factor Xa in the blood compartment. The subsequent sections on pages 61- 62 posit that salts can be synthesized from the parent compound and that prodrugs may be made to improve the properties of a molecule. Several chemical groups are mentioned in this section but there is no recognition that a prodrug is likely to be a New Chemical Entity (NCE).

6.2.3 On page 62, line 21 there is a discussion of a 'therapeutically effective amount' with the possibility of a combination with another agent that would be 'synergistic' citing a paper from 1984. The skilled pharmacokineticist would know the difficulties of combination drug development where each agent would need to show efficacy alone and that the combination would provide better efficacy. The skilled pharmacokineticist would not only be aware of this possibility but would also know that anticoagulant drugs often need to be titrated to efficacy and then possibly be dose-adjusted. This would be difficult with a combination product.

6.2.4 Successive sections starting on page 63 cite the synthetic routes required to obtain several of the previously identified compounds through page 208 where a section describing functional groups that could be added through page 262 with no explanation as to why any of them might be 'pharmaceutically acceptable'.

6.2.5 A section on 'Utility' begins on page 263. This section describes the basic pharmacology and testing of compounds, which a pharmacologist would be very familiar with.

6.2.6 A section on 'Dosage and Formulation' is presented beginning on page 268. This section listed several routes of administration, several of which the skilled pharmacokineticist would not have included in modern drug development in 2001 including pills, elixirs, and tinctures. These formulations would be unacceptable based on the method manufacture and the possible presence of alcohol as an excipient. The patent application tends to cite the 1984 edition of 'Remington's Pharmaceutical Sciences' as a standard reference text but the skilled pharmacokineticist would note that this text presents a high level summary that is directed primarily at pharmacists and not research scientists/skilled pharmacokineticists in drug development. More generally acceptable formulations are presented followed by a wide range of dose strengths and inexplicably, a discussion of combination products on page 271.

6.2.7 Claim 1 begins on page 273 through to Claim 9 on page 325 with structures and functional groups that number potentially in the hundreds. Finally Claims 10 through to 13 present pharmaceutical compositions, a method of treatment or preventing a thromboembolic

disorder, for use in therapy, and manufacture of a medicant. The skilled pharmacokineticist would recognize that these claims do not teach anything of significance about the invention.

6.3 All things considered, WO131 would have been of limited interest to a skilled pharmacokineticist in 2001. There is only information pertaining to potential formulations, dosing strengths, and dosing regimens with no supporting evidence that would permit pharmacokinetics analysis, simulations, or any other pharmacokinetics predictions.

[4]...*WO 03/026652*

7.1 I was also asked to review WO652 and consider what it teaches the skilled pharmacokineticist. Again, I have set out below my analysis of WO652.

7.1.1 In WO652 there is a 'Background of the Invention' section that includes on page 6 a useful list of desirable properties of efficacious and specific inhibitors of Factor Xa. The document states that it is 'desirable and preferable to find compounds with advantageous and improved characteristics' and lists the following factors that would have been of general interest to the skilled pharmacokineticist:

(a) pharmaceutical properties (e.g. solubility, permeability and amenability to sustained release formulations);
(b) dosage requirements (e.g. lower dosages and/or once daily dosing);
(c) factors that decrease blood concentration peak-to-trough characteristics (e.g. clearance and/or volume of distribution);
(d) factors that increase the concentration of active drug at the receptor (e.g. protein binding, volume of distribution);and
(e) factors that decrease the liability for clinical drug interactions (e.g. cytochrome P450 enzyme inhibition or induction).

7.1.2 However, the list above is simply a list of desirable characteristics for any drug. It is not specific to a Factor Xa inhibitor, nor does it describe the characteristics of any particular compound disclosed in the document. Furthermore, whilst it sets out a characteristic, e.g. solubility or permeability, it does not actually explain what is desired, i.e. high or low solubility / permeability. The skilled pharmacokineticist would therefore take nothing from this section of WO652.

7.1.3 This section is followed by a Background and Summary that presents structures and a considerable number of functional groups that goes on for 129 pages before presenting embodiments of a pharmaceutical formulation, a method for treating a thromboembolic disorder, and numerous conditions with a thromboembolic mechanism. Starting on page 131 there are several embodiments that bring up prior statements regarding a salt form, a combination product with numerous approved products including warfarin, heparin, and other drugs that should not be considered to be used in a combination product. Several embodiments then describe first and second containers to be used in the unlikely licensure of combination anticoagulants.

7.1.4 'Definitions' begin on page 134 and include discussions of racemic mixtures, preferable molecular weights, isotopes, and claims that are meant to cover claimed structures through page 168 where a section on 'Utility' begins. This section then covers much of the same material as WO131 with respect to the methods of testing compounds. The section on page 172 states that the compounds are to be administered to a mammal in a therapeutically effective amount and then inexplicably discusses possible combinations with other classes of drugs for the next 6 pages.

7.1.5 Beginning on page 180 there is a section on 'Dosage and Formulation'. Once again, the skilled pharmacokineticist would recognize that pills, powders, elixirs and tinctures would not have been acceptable dosage forms in the modern drug supply chain in 2001. On page 182 the document points out, correctly, that the dosage regimen will depend upon several factors. However, none of the expected early stage development information about physicochemical properties, solubility, permeability and information and inhibition of CYP450 metabolism is provided.

7.1.6 The section on daily oral dosage indicates that a possible range of doses could be 0.001 to 1000 mg/kg. The skilled pharmacokineticist would recognize that this range would provide a fixed dose upper of 70,000 mg for a 70 kg patient. This would be 70 grams per dose and the proposed 100 mg dosage form would require each dose to consist of 700 capsules and is obviously not possible. There are other ranges cited that are more reasonable. Pages 183-186 delineate additional routes of administration and suitable excipients. However, on pages 187-188 combination drug products come back into the narrative.

7.1.7 The remainder of WO652 consists of declarations of structures and functional groups through page 438 where the claims include presenting pharmaceutical compositions, a method of treatment or preventing a thromboembolic disorder, for use in therapy, and manufacture of a medicant are cited.

7.2 To conclude, WO652 would also have been of limited interest to a skilled pharmacokineticist in 2001. There is only information pertaining to potential formulations, dosing strengths, and dosing regimens with no supporting evidence that would permit pharmacokinetics analysis, simulations, or any other pharmacokinetics predictions.

7.3 In summary, and as mentioned above, based upon consideration of the detailed responsibilities of the skilled pharmacokineticist in the various stages of drug development in 2001, WO652 contains too little relevant information/data with sufficient detail to permit a person with CGK to conduct the necessary work.

[5] *W0131 AND W0652*

8.1 The information presented in WO131 and WO652 consists primarily of details of synthesis of potential drugs to treat thromboembolisms and addition of functional groups.

8.2 A surprising amount of emphasis is placed on combination products which is not likely to be successful as an antithrombotic drug. No information is provided that could permit the prediction of pharmacokinetic properties including half-lives, bioavailability, clearance estimates and volumes of distribution which are all important for establishing safe and effective dosing regimens.

8.3 This limited teaching of a very important component of drug development prevents the useful application of both WO131 and WO652."

Statement #2 of 2

1. *COMMENTS ON THE WITNESS STATEMENT OF DR. DAVID TAFT*

1.1 In paragraphs 28-33, Dr Taft explains his view that WO652 is directed to a skilled team including a pharmacokineticist. As I explained in my first report, WO652 contains no teaching of interest from a pharmacokinetics perspective. For example, there is no in vitro data regarding solubility, permeability, lipophilicity, intrinsic clearance, enzymes involved in metabolism, or any other information that a pharmacokineticist could use to predict what the pharmacokinetic properties would be. Further, no theory or data are provided in WO652 that would permit a skilled pharmacokineticist to learn anything about the pharmacokinetic profile of any of the molecules described in the Application.

1.2 Paragraphs 38-60 of Dr Taft's report set out some basic theory and concepts in pharmacokinetics. In general, I agree with Dr Taft's presentation of these topics, and agree that they are concepts which the skilled pharmacokineticist would have known. These sections contain basic concepts that would be presented as part of an undergraduate curriculum. However, the basic concepts alone as presented in paragraphs 38-60 would not be adequate for the practice of pharmacokinetics in the pharmaceutical industry. WO652 does not describe any of these basic pharmacokinetic concepts in any detail, or contain any teaching which would not form part of the skilled pharmacokineticist's common general knowledge.

1.3 Specifically, in paragraphs 54-60, there is a description of pharmacokinetic studies and the process of plotting concentration data to obtain a concentration versus time profile, and a presentation of several concepts and equations enumerating various pharmacokinetic parameters. All of these analyses require concentration-time data for the drug; but there is

absolutely no concentration-time data in WO131 or WO652 that would permit even the most simplistic pharmacokinetic analysis.

1.4 *Paragraphs 61-66 consist of a brief section on 'Pharmacokinetic Testing'. These tests are certainly done by pharmaceutical companies and at times result in discontinuing development of a particular drug. I agree with Dr Taft's comments that in vitro experiments can provide important information to assess pharmacokinetic properties, and that in vivo studies are used to determine pharmacokinetic parameters. However, as I explained in my first report, WO652 presents no data from any such tests or for any specific compound.*

1.5 *In Figure 6, Dr Taft presents a graph showing the volume of distribution ('**Vd**') and clearance values of certain compounds. It is notable that warfarin is shown at the lower left corner of the graph, indicating it has a low Vd and low clearance. As I explain further below, this combination of properties meant that warfarin has less than desirable characteristics with respect to time of offset due to a long half-life. The anticoagulant effect in warfarin is prolonged, meaning that patients may be susceptible to undesirable bleeding for some time after their course of warfarin is discontinued.*

1.6 *In paragraph 79 of his report, Dr Taft addresses the teaching on page 6 of WO652. He characterizes this passage as describing a list of "advanced research objectives". However, there is nothing advanced about this list. Each of the concepts in this paragraph would be known to the skilled pharmacokineticist from their common general knowledge. It is a typical list of the kinds of pharmacokinetic properties which the skilled pharmacokineticist would consider during a drug discovery project, and each of the characteristics would apply to almost all drugs. The list identifies the sort of information which the skilled pharmacokineticist would envisage gathering during any drug discovery project but provides no qualitative or numerical ranges which the skilled team should endeavour to attain in their target compound. Further, no information or data is presented in WO652 that would suggest that any of the hundreds of molecules described in the patents would be acceptable in this regard.*

1.7 *Paragraphs 81-89 focus on the desirable characteristics of a pharmacokinetic profile for a Factor Xa inhibitor. In paragraph 81, Dr Taft states that the Application teaches a pharmacokinetic profile of a low Vd and an even lower clearance. A compound which has a low Vd is merely another way of saying that it is generally retained in the blood rather than distributing into the tissues. For a compound such as a Factor Xa inhibitor which is intended to interact with a target in the blood, the skilled pharmacokineticist would know from the common general knowledge that a low Vd was desirable.*

1.8 *Dr Taft then indicates that a low Vd and even lower clearance is desirable because it will lead to a long half-life. I agree that these parameters are related in the equation given by Dr Taft. However, this reasoning has to be kept within reasonable bounds. Too long a half-life and too low a clearance may result in anticoagulant activity that is protracted. This may be undesirable because the compound will present a prolonged pharmacological effect and, for an anticoagulant, that means the potential for bleeding for a long period of time. Thus, rather than a longer half-life and lower clearance, both of these parameters should be optimized to provide peak and trough concentrations that are safe and effective in a convenient dosing interval.*

1.9 *I disagree with Dr Taft's opinion in paragraph 83 that the Application teaches the nuanced relationship between Vd and clearance that impact the peak to trough ratio. First, it is difficult to believe that the Application teaches anything that would permit a pharmacokineticist to optimize a dosing regimen since no data are presented for any compounds, nor (as I have explained above) does the Application teach any qualitative or numerical bounds for the pharmacokinetic properties. Second, there is no evidence whatsoever that any molecule identified in either patent would reduce or eliminate pre-systemic metabolism, as much as that would be desirable. Indeed, I agree with Dr Taft's statement in paragraph 85 that 'While the synthesis of a number of compounds is provided in the examples, no pharmacokinetic data specific to any one compound is presented'.*

1.10 *In the four sub-paragraphs following paragraph 83, Dr Taft appears to present some advantages which derive from the combination of a compound which has a low Vd and an even lower clearance. However, these sub-paragraphs are just restatements of compounds*

which have those properties as would be known to the skilled pharmacokineticist from the common general knowledge. The Application does not teach anything about the combination of a low Vd and an even lower clearance that would not already have been known.

1.11 *Paragraph 86 implies that a skilled pharmacokineticist would have anticipated that a compound that was synthesized in gram quantities would be destined to become a significant new medicine. Upon my review of the Application, I did not identify the synthesized amount of Example 18. I do not think [sic].*

1.12 *In paragraph 90, Dr Taft states that 'Example 18 does not expressly state that the scale-up was conducted in order to prepare material to permit preclinical testing in animals'. However, in paragraph 96 he goes on to suggest that the synthesized amount would suggest that 'initial pharmacokinetic results were sufficiently promising to move to larger-scale studies'. It is mere speculation to suggest that Example 18 would possess any specific pharmacokinetic characteristics, whether desirable or otherwise. A further statement that apixaban would have a low (small actually) Vd and 'even lower clearance' is not credible since there is absolutely no evidence, e.g., data, that Example 18 would possess these characteristics.*

1.13 *In paragraph 97 there is a statement that apixaban's pharmacokinetic profile is taught in the Application as follows in A-D. Unfortunately, there is nothing taught in the patent regarding (A) concentrations of drug, (B) a long half-life, (C) reduced systemic metabolism, or (D) decreased potential for side effects since no evidence (data) are presented. There is no chance that the in vivo pharmacokinetic profile can be determined with any specificity using the structure.*

APPENDIX 16

Abridged Written Evidence of Dr Young

Statement #1 of 2.[25]

The skilled person/team

12. *I believe that the Patent would be of interest to a skilled team involved in drug discovery. Such a skilled team would include expertise in medicinal chemistry, biology and/or biochemistry, pharmacology, pharmacokinetics, toxicology and clinical medicine.*
13. *The Patent's focus is on the structure and synthesis of new molecules and therefore the skilled medicinal chemist would be a key member of the skilled team. The skilled medicinal chemist would typically have a degree and PhD in chemistry and/or several years' experience working on drug discovery in industry. Medicinal chemists work on a range of drug discovery programs during their careers and the skilled medicinal chemist may, or may not, have experience of the target of the particular drug discovery program (in this case factor Xa). If the skilled medicinal chemist had no experience of work on factor Xa, they would gain such knowledge through talking to other members of the skilled team and by reading relevant literature, such as the review articles that I refer to in paragraphs 16 to 53 below, and attending conferences. Learnings and precedent from other protease enzymes in general and trypsin like serine proteases (such as trypsin and thrombin) in particular, would provide additional sources of knowledge.*
14. *The rest of this witness statement is written from the perspective of the skilled person described in paragraph 13 above, who I refer to as "the medicinal chemist" or "skilled person".*
15. *It has been explained to me that what is important is not my own personal knowledge and views in relation to the issues addressed in this witness statement but those of the relevant skilled person. I believe that, except where I have indicated otherwise, the knowledge and views expressed in this witness statement would have been representative of the views of the skilled person at the Priority Date.*

Common general knowledge of the medicinal chemist
Sources of CGK

16. *At the priority date of the Patent, the background CGK of the medicinal chemist would have been reflected in various publications such as:*

A. *An Introduction to Medicinal Chemistry by Graham L. Patrick (2nd edition, 2001);*

B. *Burger's Medicinal Chemistry and Drug Discovery edited by Manfred E. Wolff (5th edition, 1995);*

C. *Comprehensive Medicinal Chemistry. The Rational Design, Mechanistic Study and Therapeutic Application of Chemical Compounds. Six volumes. Edited by C.*

D. *The Journal of Medicinal Chemistry;*

E. *Bioorganic & Medicinal Chemistry Letters;*

[25] The papers annexed to the statement are not included.

F. *Expert Opinion on Therapeutic Patents;*

G. *Current Medicinal Chemistry;*

H. *Current Topics in Medicinal Chemistry; and*

I. *Annual Reports in Medicinal Chemistry.*

17. *Except where I have stated otherwise, I believe that the information set out below in this section would have been part of the CGK of the medicinal chemist at the Priority Date. Where I use the present tense, it should be understood that my account is of the CGK at that date. Where appropriate, I have provided references to important scientific articles and reviews.*

Overview of drug discovery and development process[1]

18. Research aimed towards the discovery of new drugs is a highly complex, multi-disciplinary empirical process with elements of trial and error, which means that drug discovery is difficult, expensive and time-consuming. In 2001, it would typically take a minimum of 2– 3 years to go from the start of a project to the identification of a clinical candidate, although the vast majority of projects would not deliver a clinical candidate. Even then, of these candidates the vast majority would fail to progress through clinical trials, which themselves can take up to a further 10 years. It would not be unusual for a medicinal chemist to spend their entire 30–40 year career synthesising compounds without ever having worked on a marketed drug.

19. *In 2001, the drug discovery process typically encompassed a number of stages:*

A. *The first stage, often referred to as "Target Discovery" (or "Target Identification"), involves the identification of a biological target or pathway that could potentially play a role in the disease. In the case of thrombosis, it was hypothesized that selective intervention, by targeting a single enzyme, within the blood coagulation pathway could lead to anticoagulant medicines with improved safety profiles and lesser need for monitoring. Early research identified thrombin as an initial target of interest and later factor Xa emerged as an additional target for intervention (Leadley, Appendix RY5);*

B. *it would be necessary to identify a compound (or one of a class of compounds) that might be promising for further development based on in vitro potency (in a factor Xa assay utilising a chromogenic or fluorescent substrate), blood based anticoagulation (measuring, for example, the extension of Prothrombin Time in a commercial kit utilised to monitor warfarin therapy) and possibly selectivity against any key off-target proteins, such as others in the blood coagulation cascade. Preliminary results from in vitro DMPK assays could also be used to prioritise chemical series if the data were available;*

C. *if a promising compound/class of compounds was identified, the skilled medicinal chemist would then synthesise variations around the compound(s) and test their potency, selectivity and DMPK properties in the hope that it would be possible to build up an idea of SAR (Structure-Activity Relationships) and SPR (Structure Property Relationships) to enhance activity (SAR) and efficacy (SPR). In 2001, it was common for chemistry teams to employ techniques of multiple parallel synthesis to generate arrays or libraries of compounds to expedite hypothesis testing and to delineate SAR.*

[1] *To prepare paragraphs 18 to 28, I was provided with text that I am told was taken from the Statement of Case of Common General Knowledge that was agreed between the parties in the parallel litigation in the United Kingdom. I have amended this text and incorporated it into this witness statement in paragraphs 18 to 28.*

D. *using the SAR and computational modelling to narrow the choice of potential compounds to synthesise, the skilled team would synthesise and test compounds in the hope of identifying molecules with sufficiently good potency, anticoagulant activity, selectivity and*

in vitro DMPK properties to be potentially useful as a drug;

E. *the most promising compounds would then be selected for in vivo testing and their synthesis scaled up to furnish necessary quantities of material. These tests would include in vivo DMPK studies and efficacy in an animal model of disease;*

F. *the most promising compounds from the in vivo testing (if any) would then move on for further DMPK and toxicology screening; and*

G. *if any compound was predicted to be sufficiently safe and effective in humans, with appropriate pharmaceutical properties (such as solubility, stability) the drug candidate would be declared, signalling an intensification of efforts to produce the larger quantities of drug substance necessary for further enabling studies and clinical trials.*

Proteins

20. Proteins are large molecules that perform a vast array of functions within organisms including *catalysing reactions, DNA replication, responding to stimuli, providing structure to cells and transporting molecules. Proteins differ from one another primarily in their sequence of amino acids, which is dictated by the nucleotide sequence of their genes. There are 20 proteinogenic amino acids commonly encoded in Nature, which each have the same fundamental structure, composed of a central carbon attached to a carboxylic acid, an amino group, a hydrogen atom and a variable fourth group, known as the side chain. With four substituents, this carbon is chiral, that is two mirror image arrangements are feasible, although proteinogenic amino acids all possess the L-configuration, most commonly termed S using the Cahn-Ingold-Prelog priority rules (cysteine is one exception due to the increased mass of sulfur). The carboxylic acid and amino groups form peptide bonds (formally the product of a dehydration reaction), which repeat to assemble the amino acid main chain. The side chains project from this main chain. Combinations of amino acids are termed peptides, from dipeptides (2 amino acids), tripeptides (3) up to oligo- (~10 to 50) or polypeptides (50+). Together, these longer sequences make up proteins, which are fundamentally characterised by their primary peptide sequence. A protein will have a defined 3-dimentional structure based on the sequence of the amino acids and their intermolecular interactions. The amino acids can be coded using 1 or 3 letter codes (Alanine, for example, is referred to as Ala or A) and this helps to describe the amino acid sequence in a protein, conventionally numbered from the N-terminus (amino end) to the C- terminus (carboxy end).*

Enzymes

21. *Enzymes are classes of proteins which catalyse over 5,000 biological reactions by accelerating the conversion of substrates to products. This can be achieved by lowering the activation energy for the reaction through stabilisation of the transition state, providing a cofactor to deliver atoms or electrons, or particular functionality in side chains reversibly participating in the necessary chemistry. Without enzymes, Nature's chemical reactions would be too slow to be useful. Enzymes act as a surface or focus for the reaction, bringing the substrate or substrates together and holding them in the best position for reaction. The reaction takes place, catalysed by the enzyme, to give products which are then released. Catalysis by an enzyme is mediated by a region of the protein termed the active site. The enzyme's natural substrate is recognised through complementary binding at the active site and the relevant reaction is catalysed. Only substrates that bind to the enzyme active site are efficiently turned over by the enzyme.*

[Diagram not included in judgment.]

Serine Proteases

22. Since enzymes catalyse a range of different reactions, they can have very different structures. Enzymes are first grouped according to their function; for example, proteases, which cleave peptide bonds, phosphatases, which remove phosphate groups, and methyltransferases, which transfer methyl groups from a co-factor.

23. There are four major classes of protease enzymes (aspartyl, serine, cysteine and metallo) that selectively catalyse the specific hydrolysis of peptide bonds through the facilitated delivery of water

to a particular site in the substrate polypeptide sequence. The catalytic mechanism that enables the delivery of water is different for each class, but typically involves nucleophilic attack on the scissile amide bond of the substrate (a covalent bond that can be broken by an enzyme) by a specific amino acid residue of the enzyme or an activated water molecule. For example, serine and cysteine proteases employ an active site nucleophilic serine or cysteine residue to mediate the cleavage of the peptide bond through a transient covalent intermediate that is hydrolysed by water. Aspartyl proteases have active site aspartic acid residues and metalloproteases have a metal ion in the active site to enable water delivery to the stabilised transition state. Within a given mechanistic family, the catalytic apparatus is very similar but there are likely to be differences in the surrounding architecture of protein sequences, forming pockets, that enable specific recognition of the natural substrates to enable preferential binding.

Enzyme Inhibitors

24. Molecules that interact with an enzyme and reduce its activity by influencing the binding of substrate and/or the number of reactions the enzyme turns over per unit time are known as inhibitors. There are various mechanisms through which enzyme inhibitors can act.

Competitive (reversible) inhibitors

25. The dynamic binding interactions between substrate and enzyme have to be properly balanced so that they are strong enough to hold the substrate(s) at the active site of the enzyme long enough to allow the reaction to take place but are weak enough to allow the products to leave (otherwise the enzyme would become "clogged up"). A molecule that binds to the enzymatic binding site, thus competing directly with a normal substrate for an enzymatic binding site, can function as a competitive inhibitor. A competitive inhibitor usually bears some features of the substrate or mimics it to the extent that it specifically binds to the active site but differs from the substrate enough to be chemically unreactive (or react very slowly). The effect of a competitive inhibitor is reversed by increasing the concentration of substrate because the frequency of successful collisions between inhibitor and active site is reduced. A competitive inhibitor therefore acts by reducing the concentration of free enzyme available for substrate binding.

26. A general model for competitive inhibition is given by the following scheme, in which the element denoted "DRUG" is shown as a competitive inhibitor for the substrate

[Diagram not included in judgment.]

Non-competitive, reversible (allosteric) inhibitors

27. *These compounds bind into an allosteric site (i.e. a binding site distal from the active site of the enzyme) which changes the affinity of the enzyme for its substrate by triggering a change in the 3D shape of the active site. The inhibitor may bind reversibly, in which case the active site of the enzyme will return to the correct 3D shape for catalysis. Many enzymes are regulated naturally by allostery.*

[Diagram not included in judgment.]

Covalent inhibitors

28. An inhibitor may bind to the active site (via, for example, the formation of a covalent bond) and permanently or reversibly block substrate from binding or inactivate the catalytic apparatus (such as by reaction with the serine residue in serine proteases). Irreversible inhibitors typically bind in the active site rather than allosterically, since the amino acids responsible for catalysis are often those that covalently bind to the inhibitor. A reversible covalent inhibitor will from a covalent bond with the protein, but in such a fashion that it might only be transient and readily hydrolysed back to regenerate the active form of the enzyme. An example of an irreversible inhibitor would be an alpha-bromoketone that alkylates the hydroxymethyl serine side chain, a reversible inhibitor could be a ketone that forms a hemi-ketal with the serine side chain.

[Diagram not included in judgment.]Binding sites in protease enzymes

29. *Factor Xa belongs to the class of enzymes known as trypsin-like serine proteases. The action of factor Xa in the coagulation cascade can directly be inhibited by the binding of a molecule at the factor Xa substrate binding site or binding pocket. In addition, indirect inhibition of factor Xa can occur by remote binding (e.g. by heparins or modified versions thereof) or through modulation of metal binding through interference with gamma-carboxy glutamate (Gla-) formation by warfarin and related compounds (Leadley, Appendix RY5).*
30. *To describe the binding site of protease inhibitors, the commonly used convention is to number sequentially, towards the N-terminus of the enzyme sequence from the site of cleavage, the binding pockets that recognise residues with characteristic side chains on substrate peptides. By convention, these pockets are termed S1, S2, etc. The groups of the substrate that bind to these pockets are termed P1, P2, etc. Pockets binding residues towards the C-terminus, or the substrate are labelled S1', S2' and so forth towards the C-terminus away from the cleavage site (Leung, Appendix RY6).*

[Diagram not included in judgment.]

31. *In many proteases the S1 pocket is a key recognition site and often termed the primary specificity pocket. In the case of trypsin-like serine proteases (including fXa, trypsin and thrombin) this pocket recognises basic residues such as those on the sidechains of arginine and lysine. Binding in the further sequential pockets (S2, S3, etc.) usually defines specificity (in terms of substrates recognised) or selectivity of inhibitors versus related proteases in the class (Leung, Appendix RY6).*

The Factor Xa binding site (S1-S4)

32. *The structure and topology of the factor Xa binding site was understood by September 2001, although difficulties of generating routine liganded X-ray crystal structures remained:* "In the case of fXa several structure-based drug design strategies have been followed because of the difficulty in growing fXa co-crystals routinely". *Some companies were progressing with X-ray crystal structures and/or using surrogates, such as trypsin, to understand likely binding modes. (Maignan, Appendix RY10)*

33. *The features of the active site of factor Xa pertinent to drug design were reviewed in detail by Maignan and Mikol (M&M) (Maignan, Appendix RY10), noting* "three main areas used in the substrate recognition and several side pockets, which can be used for drug design... Most of the active site lies on the surface of the protein with the exception of the S1 pocket, which extends about 8Å deep into the core of the protein" *(Figure 6). (Maignan, Appendix RY10).*

[Diagram not included in judgment.]

34. *M&M describe the active site of factor Xa as follows:* "The S1 pocket is the main anchoring point and accommodates a positively charged lysine or arginine side chain from the substrate (P1 residue). It is narrow cleft with planar hydrophobic walls and a negatively charged Asp189, which engages in a salt bridge with the substrate, lies at the bottom of the pocket. The pocket is somewhat larger than the lysine or arginine side chain and can accept bulkier groups such as aromatic rings. Another important feature of the S1 pocket is the presence of a buried water molecule located above Tyr228, which forms hydrogen bonds with main chain carbonyl oxygens of Val227 and Trp215*." (Maignan, Appendix RY10)*

35. *Furthermore, the review describes the S4 pocket (suggested as an agglomeration of S3 and S4), as a surface cleft formed by the hydrophobic resides Trp215 (floor) with walls of Tyr99 and Phe174. Whilst this box usually accommodates a hydrophobic residue, there was recognition that the named side chain residues* "are quadrupolar and can participate in favourable interactions with a positive charge." *Backbone carbonyl groups of Lys96 and Glu97 and the side chain of Glu97 were highlighted as potential further charge stabilizers in the region. Already a variety of structural features of factor Xa inhibitors were evidently binding as P4 surrogates in this pocket and the implications of this towards selectivity were noted*, "since it differs significantly from most trypsin-like serine proteases." *(Maignan, Appendix RY10)*

The structure of factor Xa inhibitors

36. *By September 2001, it was recognised that many factor Xa inhibitors had a common structural theme. This was described as:* "the P1 group which binds in the S1 pocket, a linker or central scaffold designed to project the substituents appropriately into the pockets and the P4 group which interacts with the S4 pocket." *(Maignan, Appendix RY10)*
37. *The nature of the scaffold or core, connecting pendant P1 and P4 groups in an appropriate orientation was described by Zhu and Scarborough who noted* "the potent factor Xa inhibitors generally have L-shaped conformations. P4 and P1 elements must have almost a 90° turn to achieve optimized interactions with S1 and S4 pockets of factor Xa. The S1 pocket of factor Xa is much more sensitive than the S4 pocket to ligand structural variations." *(Zhu 2000, Appendix RY16) This reflects that it would have been understood by the skilled person that the S4 binding pocket allowed for considerable variability in the structures of P4 elements. Often the scaffold or core was based on a ring and amide functionality is common, reflecting opportunities for rapid optimisation using readily available monomers (either commercial or using short synthetic routes) for P1 and/or P4 exploration and optimisation. The core was not necessarily just a connector, as substituents could make productive interactions with the factor Xa protein (e.g. carbonyls with Gly218) or influence the physical properties of the molecule as a whole. (Zhu 2000, Appendix RY16)*

The importance of neutrality or modulated basicity in factor Xa inhibitors

38. *Early factor Xa inhibitors, such as DX-9065A shown below, had relied on a basic amidine group in the P1 position to bind to the Asp189 of the S1 pocket of factor Xa to provide potent factor Xa inhibitors. (Al-Obeidi, and Zhu 1999, Appendices RY2 and RY17) The predicted pKa values[2] of this compound are as follows: Naphthyl carboxamidine 12.58 (basic), acetamidine 11.70 (basic) and carboxylate 4.36 (acidic).[3]* =

[Diagram not included in judgment.]

[2] *The pKa is a measure of basicity/acidity. pKa is the negative logarithm, base 10, of the dissociation constant, Ka, reflecting the pH at which the unionized species and its conjugate base or acid species are equal.*
[3] *All pKa values were obtained for given compounds or pertinent fragments using SciFinder, where they were calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2022 ACD/Labs), accessed on 10 March 2022.*

39. *However, by September 2001, there was a desire to provide compounds without groups exhibiting highly basic character. This quote from the Al-Obeidi review is typical of various commentaries highlighting a desire to move towards at least reduced basicity (i.e. pKa <11]), if not neutral molecules (i.e. molecules with a pKa that is so low that no nitrogen atoms likely to be protonated at pH 7.4 (physiological pH) and thus be positively charged):* "Although the presence of a strongly basic group, in particular the amidine function, is in many cases essential for potency, it may hinder oral bioavailability and enhance haemodynamic toxicity.*" (Al-Obeidi, Appendix RY2) By 2001, the role of potassium channels such as the human Ether-a-go-go Related Gene (hERG) in cardiotoxicity was increasingly appreciated, and the risk that basic lipophilic amines could impair the function of the channel, leading to compromised blood flow (haemodynamics). Shortcomings in oral exposure for charged, basic, molecules of similar size to contemporary factor Xa molecules were well known as the reviews suggested. Removing charge and optimising lipophilicity[4] were prescribed as methods of improving oral pharmacokinetic exposure. (Zhu 2000, Appendix RY16)*

40. *In a prescient summary, Zhu & Scarborough described the compromises and innovations that were required in the optimisation of oral small molecule inhibitors of factor Xa:* "Thus, from an in vivo efficacy perspective, high aqueous solubility (log D < 0) and low plasma protein binding are preferred. From a pharmacokinetic perspective, moderate lipophilicity and good aqueous solubility

(preferably log D in the range of 1-4) are preferred. Therefore, in order to obtain clinically viable oral factor Xa inhibitors, very careful and systematic approaches to optimize in vitro potency (preferably Ki < 1 nM), specificity, and balanced physicochemical properties are necessary to achieve both good pharmacokinetic profiles (high oral bioavailability and long t-1/2) and antithrombotic efficacy." *(Zhu 2000, Appendix RY16)*

41. *The opportunities of combinatorial chemistry enabled the production of large numbers of molecules for screening, to exploit the enhanced capacity of high throughput screening technologies. However, attention to the physicochemical properties of the molecules was often not considered. The seminal paper from Lipinski et al, entitled* "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings", *suggested constraints on lipophilicity, molecular weight and hydrogen bonding features to improve the likelihood of achieving solubility and permeability (contributing to more likely successful outcomes in drug development) (Lipinski 97, Appendix RY8).*

42. *The Lipinski paper, is best known for the section resulting from the analysis of simple features that distinguished drugs (in the USAN list[5]) from molecules synthesised in the post- high throughput screening era. Lipinski established guidelines based on figures derived from90th percentile of the distribution in the drug set that were rounded to the famous fives, of the "*Rule of 5*" namely*:

    A. *Molecular Weight <500 Daltons,*

4. *Lipophilicity represents the ratio at equilibrium of the concentration of a compound between two phases, an oil and a liquid phase (Bohnert and Prakash, 2012), typically 1-octanol and water/aqueous buffer in drug discovery. A compound's solubility, ability to permeate biological membranes and consequently its oral bioavailability through absorption from the gastrointestinal tract are all related to its lipophilicity.*

5 *The USAN list is the United States Adopted Name list which is a list of names of drugs and candidate drugs assigned by the USAN Council. The USAN Council is co-sponsored by the American Medical Association, the United States Pharmacopeial Convention and the American Pharmacists Association.*

    B. *cLog P[6] (calculated Partition coefficient) <5*
    C. *number of hydrogen bond donors <5*
    D. *hydrogen bond acceptors <10* [7]

43. Lipinski's analysis demonstrated that if a molecule violated no more than one of these criteria it engendered an improved likelihood of achieving solubility and permeability. Although it should be noted that a molecule of MW 498 and cLog P of 4.9, whilst being compliant with the rules, represents a combination towards the higher end of both percentile ranges, so actually has a low chance of achieving solubility and permeability. Lipinski's paper was first published in 1997, (Lipinski 97, Appendix RY8) reprised in 2001 (Lipinski 01, Appendix RY9) by which time a wider awareness of the inferences was entering common practice.

44. *By September 2001, it was well established that it was not necessary for a factor Xa inhibitor to have a basic group in the P1 position to provide potency. The M&M review clearly describes neutral P1 groups discovered by Lilly, Zeneca and RPR and rationalises their binding and states that* "the formation of the salt bridge to Asp189 is not an absolute prerequisite to obtain inhibitors with inhibition constants within the nanomolar range." *(Maignan, Appendix RY10)*

45. *A further insightful commentary from Zhu & Scarborough described their understanding and likely experience of the binding modes of factor Xa inhibitors and some likely misconceptions or misunderstandings of binding modes:* "However, due to the symmetric nature of the S1 and S4

pockets (both S1 and S4 pockets can bind to hydrophobic or positively charged motifs), it is sometimes not obvious how to predict the binding modes (orientations) of specific inhibitors with factor Xa. Additionally, a subtle structure change of a lead structure can reverse the binding orientation. It might also be possible for an inhibitor to have dual binding modes. Thus, within a series it may be difficult to carry out systematic structure-activity relationships if the binding orientation changes due to very subtle structural modifications or an incorrect binding mode is presumed*." (Zhu 2000, Appendix RY16). Techniques of combinatorial chemistry were ideally suited to the rapid exploration of the potential variations in binding modes and to explore novel motifs in a prospective manner (Betz and Herron, Appendices RY3 and RY4).*

Significant factor Xa inhibitors known in September 2001

46. *The following 6 compounds are chosen to represent key developments and examples where clear advancement was reported, as of September 2001. Each, in addition to primary literature and/or patent disclosure, was highlighted in one or more of review articles, including the series of monographs in a special issue of Current Medicinal Chemistry in 2001, and expert opinions on patents. All pKa values shown below are from ACD calculations as described earlier in the footnote to paragraph 38.*

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[6] *Lipophilicity, or intrinsic lipophilicity, is typically referred to as Log P (logarithm (base 10) of Partition Coefficient, P). Calculated log P (cLog P) describes a calculated value for lipophilicity using one of many methods available. CLogP (or CLOGP) is typically how clog P is represented when calculated using (copyrighted) Daylight calculator; see: https://www.daylight.com/dayhtml/doc/clogp/. If a molecule had neither an acidic or basic centre, the lipophilicity will not vary with the pH of the aqueous buffer in the partitioning experiment. Thus, the Partitioning of the molecule between immiscible aqueous and organic layers is a constant irrespective of pH (pH is the log (base 10) of the hydrogen ion concentration times -1). However, when the molecule is basic or acidic (and thus can be ionised) the neutral and protonated (bases) or deprotonated (acids) forms will have differing preferences for the environments. It is the Distribution of all forms between the layers that defines the behaviour – and this is described by the Distribution coefficient (commonly expressed as log D at a specified pH, often estimated at pH 7.4 or physiological pH). At pHs above (bases) or below (acids) the pKa and asymptote is apparent, representing the log P value of the unionised molecule. Partition and Distribution coefficients can be measured or, alternatively, be estimated using predictive software that was readily available and used in 2001.*

[7] *The hydrogen bond donor and hydrogen bond acceptor counts were prosaically calculated as the "sum of OHs and NHs" (nitrogen and oxygen atoms with attached hydrogen able to donate within a hydrogen bond) or the "sum of Ns and Os" for acceptors – where the lower case "s" in each designates the likely multiple occurrences of each atom.*

Example 1 DPC423

47. *The publication of DPC 423 in J Med Chem in early 2001 (Pinto, Appendix RY13) generated a lot of interest in the field, given the non-amidine structure, reduced basicity (pKa ~8.67), high potency, and oral efficacy; the Ries review stated* "The discovery of this compound may have been the most important progress in the field of orally active FXa inhibitors during the last 18 months." *(Ries, Appendix RY15). The structure of this molecule and the structure activity relationship (**SAR**) leading up to it were noted in additional reviews (Zhu 2000 and Betz, Appendices RY16 and RY3)[Diagram not included in judgment.]*

Example 2 Lilly S1 methoxy phenyl

48. *Lilly's identification of the (pyridin-4-yl)piperidine/methoxybenzamide combination presented an early example of a reduced basicity compound (pKa ~ 10.88), which was modelled to bind to factor Xa with the methoxy phenyl in the S1 pocket. (Masters, Appendix RY11) This was contrary to a reported hypothesis that Example 4 (described below) was likely to bind with the pyridine in S1 in an otherwise neutral structure and consistent with the commentary of Zhu and Scarborough at paragraph 45 above. The significance of this molecule and/or closely related examples in the series were noted in Maignan, Ries, Zhu 2000, Zhu 1999, Betz and Rai, Appendices RY10, RY15, RY16, RY17, RY3 and RY14*

Example 3 Fidexaban

49. *Fidexaban (ZK 807834, CI 1031) was an example of a dibasic (pKa values 12.75 (carboxamidine) and 10.65 (dihydroimidazole)) and monoacidic (pKa 3.25) combination in a factor Xa inhibitor. This potent example also achieved modest oral exposure, using a charge combination (2 bases, one acid) often used in thrombin inhibitors, enabling demonstrable efficacy following oral dosing despite the modest absorption. (Light, Appendix RY7). Contemporary understanding, highlighted by Lipinski, (Lipinski 97, Appendix RY8) noted the potential for some molecules to cross membranes on transporters, which is a potential rationale for the observed oral efficacy. This molecule was noted in Maignan, Ries, Leung, Zhu 2000, Al-Obeidi, Light, Zhu 1999, Betz and Rai, Appendices RY10, RY15, RY6, RY16, RY2, RY7, RY17, RY3 and RY14.*

Example 4 Zeneca

50. *This Zeneca example was noted (Al-Obeidi, Appendix RY2) as a reduced basicity molecule (pKa 10.88) with potent factor Xa inhibition, good anticoagulant activity and demonstrable in vivo efficacy. Ries reported that* "it is reasonable to assume that the 6- chloronaphthylsulfonyl moiety occupies the S4 pocket and the pyridine interacts with the S1 subsite of FXa*" (Ries and Al-Obeidi, Appendices RY15 and RY2). This assumption was challenged by Zhu and Scarborough who performed their own modelling studies that suggested the opposite binding mode, with the neutral* "arylsulphonamide oriented into S1" *(Zhu 2000, Appendix RY16). This molecule and/or pertinent SAR around it was noted in Ries, Zhu 2000, Al Obeidi, Zhu 1999, Betz, Rai, Appendices RY15, RY16, RY2, RY17, RY3 and RY14.*

[Diagram not included in judgment.]

Example 5 RPR200443

51. *The RPR200443 compound illustrates a development compared with above Example 4 in that the 5-azaindole motif engenders further reduced basicity (pKa ~8.13) in comparison with the piperidylpyridine of Example 4, with both potency and oral efficacy reported with this molecule. (Pauls, Appendix RY12) Likewise, in comparison with Example 4, this compound could potentially bind either way around between S1 and S4. This molecule and/or pertinent SAR around it was noted in Maignan, Ries, Al Obeidi, Zhu 1999, Betz, and Pauls, Appendices RY10, RY15, RY2, RY17, RY3 and RY12*

[Diagram not included in judgment.]

Example 6 RPR120844

52. *Of further note is the related RPR 120844 with the methoxynapthyl motif that was reported in Rai, Appendix RY14 to bind with the amidine (pKa 10.88) in S1 of trypsin, but in factor Xa this is an example of a molecule that could potentially bind in either mode as some SAR suggested (Pauls, Appendix RY12). This molecule and/or pertinent SAR around it was noted in Maignan, Ries, Zhu 2000, Al Obeidi, Zhu 1999, Rai and Pauls, Appendix RY10, RY15, RY16, RY2, RY17, RY14 and RY12.*

[Diagram not included in judgment.]

Summary

53. *In September 2001, considerable efforts to find small molecule, non-peptidic factor Xa inhibitors were in progress, with many publications and patents from a growing number of organisations noted in various contemporary reviews of progress, as well as the attractiveness of the factor Xa target (Leadley, Appendix RY5). The desire to pursue series of factor Xa inhibitors that did not contain a strongly basic (commonly an amidine) moiety was highlighted and progress was noted in reviews. By this time, several reduced basicity and non-basic P1 groups had been published, their likely orientation supported by modelling studies, crystal structures and extrapolation from pertinent data in thrombin (another trypsin- like serine protease with a similar S1 pocket). (Rai and Tucker,*

Appendix RY14 and RY18). The variety of structurally distinct binding groups in factor Xa inhibitors is attributable to the broad-brush approaches of combinatorial chemistry, whereby structural diversity was pursued to test possibilities, accessible through the high-throughput nature of contemporary technologies for multiple parallel synthesis. Thus tens, even hundreds, of compounds were quickly synthesised, purified, and prepared for testing, enabling the identification of new chemical structures with unique binding modes in the factor Xa S1 and S4 pockets.

THE APPLICATION AND APIXABAN

54. *The Application is entitled "Lactam-containing compounds and derivatives thereof as factor Xa inhibitors". Pages 1 to 5 of the Application set out several chemical structures which are disclosed in earlier patents and patent applications. At the foot of page 2 there is a reference to WO 131 that I discuss below. Pages 5 to 6 briefly describe the role factor Xa and that inhibition of factor Xa may produce an anticoagulant effect. Page 6 then states that is it desirable to find efficacious and specific inhibitors of factor Xa and sets out a list of desirable pharmacological properties commensurate with the translation of potency into efficacy.*
55. *At the end of a section headed "Summary of the invention" on page 8, the Application sets out a broad Markush formula to describe the compounds that are the subject of the Application: P4-P-M-M4. This formula is described in detail in the section headed "Detailed description of the preferred embodiments".*
56. *Pages 8 to 21 describe an embodiment that I will refer to as "embodiment 1" (it is denoted as [1] at page 8, line 9). Although, as in my experience is typical in patents, the Markush formula for embodiment 1 is broad, the skilled medicinal chemist would recognise that it is focussed on a particular class of compounds – namely those with lactam substituents (or their sulfonyl congeners, known as cyclic sulfonamides or sultams). This is apparent from the excerpts from embodiment 1 that I describe below:*

[Diagram not included in judgment.]

57 *Summarising the above: Each compound described by the formula P4-P-M-M4 contains an M4 group described by the formula -Z-A-B. B, in the formula -Z-A-B, is defined as a lactam (i.e. a carbocyclic ring comprising an amide) or a sulfur containing analogue of a lactam.*
58. *Embodiment 2, described on pages 21 to 30, covers a narrower class of compounds defined by the fused bicyclic ring formula below (Formula II):*

[Diagram not included in judgment.]

59. *As for embodiment 1 described above, the M4 group is defined as a lactam (or sulfur containing analogue).*
60. *Embodiment 3, described on pages 30 to 45, provides examples of the ring systems that make up Formula II above (at pages 30 to 36), as well as examples of the groups at position P4 (at pages 36 to 40). As with embodiments 1 and 2, the compounds of embodiment 3 all contain a lactam (or its sulfur containing analogue), as is set out on page 41.*
61. *The subsequent embodiments describe narrower series of compounds. For example, embodiment 5 provides examples of lactam substituents on pages 59 to 61. Embodiment 6 provides examples of the fused bicyclic ring of Formula II (pages 63 to 65), P4 (or G) substituents (page 66) and lactams (pages 66 and 67).*
62. *Embodiment 7 (pages 67 to 68) describes a narrower series of compounds comprising a 1,4,5,6-tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one core (also known as pyrazolopiperidone) (shown below), a range of P4 (or G) substituents and one of two lactams (shown below).*

[Diagram not included in judgment.]

63. *I note that the pyrazolopiperidone core contains a lactam group. However, I consider the focus of the Application to be the lactam substituents that I describe above and that are present in all of the embodiments that I describe above. Furthermore, I note that the 2- pyridone moiety employed as the distal group of the preferred lactam substituent (embodiment 7, page 68, right hand lactam substituent*

above) is commonly described as a lactam and this tautomer is locked by the N-substitution.

64. *Embodiment 8 then lists a series of 74 compounds that are said to be preferred. Although the structures are not provided for these compounds, the skilled medicinal chemist could readily analyse the structures of the compounds based on their chemical names. This is particularly the case given that the skilled medicinal chemist would quickly recognise that the compounds listed in embodiment 8 are pyrazolopiperidones of the type shown in embodiment 7.*
65. *The figure below sets out an analysis of the frequency of particular motifs appearing in the structures of Embodiment 8, noting the common core and frequently used variations in the P1, P4 (proximal and distal rings) and the 3-position (R3) substituents.*

[Diagram not included in judgment.]

66. *The 74 compounds of embodiment 8 represent a subset of the exemplified compounds that I discuss below (see paragraphs 70 through 74). The 74 compounds all have a common 1,4,5,6- tetrahydro-7H-pyrazolo[3,4-c]pyridin-7-one core. 70 of these compounds are constructed with the recognisable combination of this core, an aryl lactam P4 substituent, known P1 binders (such as methoxyphenyl) and variations at R3 (with a focus on trifluoromethyl and carboxamide). Based on the repeated use of this core and an analysis of the frequency of the substituents used (such as that shown above), a skilled medicinal chemist would recognise the preferred substituents and where changes were focussed to secure potency and/or optimal pharmacological and physicochemical properties.*
67. *From page 76 to page 129, the Application describes further embodiments 9 to 15. As with embodiments 1 to 8 described above, each of embodiments 9 to 15 comprises a lactam substituent, but whereas the later embodiments in the series of embodiments 1 to 8 are focussed on compounds with a fused bicyclic core, embodiments 9 to 15 are focussed on compounds with a monocyclic core.*

68. *Pages 143 to 168 describe various synthetic schemes for the synthesis of the types of compounds described in the Application. The synthetic schemes could be readily carried out by the skilled medicinal chemist. Pages 168 to 172, under the heading "Utility" describe a method of measuring the potency (Ki) of factor Xa inhibitors and a method of assessing the anticoagulant effect of factor Xa inhibitors in a rabbit, both of these methods would be well known the skilled team.*
69. *On page 170 at lines 21 to 22, the Application states "Compounds tested in the above assay are considered to be active if they exhibit a Ki of ≤ 10μM." Although a compound with a Ki as high as 10 μM is unlikely to be a therapeutically effective factor Xa inhibitor, such a compound does show an inhibitive effect and would be useful as an early "hit" in a drug development program from which more potent inhibitors could be developed and SAR delineated (see paragraph 19). This paragraph of the Application then goes on to list more preferred ranges of Ki and states that the "still more preferred compounds" have Ki's of ≤ 0.001 μM. I agree that skilled team would have been looking for compounds with this range of Ki. Finally, this paragraph states that* "a number of the compounds of the present invention were found to exhibit Ki's of ≤ 10 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors". *The skilled person would understand this to mean that the inventors had tested some of the synthesised compounds and found them to be effective factor Xa inhibitors.*
70. *Pages 188 to 298 of the Application describe 140 example compounds. For 110 of these compounds, details of the synthesis and characterisation are provided.[8] The skilled medicinal chemist would understand that the inventors had made each of these 110 compounds. In a similar fashion to the analysis of embodiment 8 above, a frequency analysis of the structural motifs in the 110 example compounds is presented below.*

[Diagram not included in judgment.]

71. *All the examples incorporate a lactam or sultam substituent in the P4 position and the examples are clearly focussed on the distal piperidone/pyridone lactam motif at the P4 group. 72 of the examples have a pyrazolopiperidone core and the above analysis is reflective of the other cores and connectivities explored by the inventors, such as the monocyclic cores described in embodiments 9 to 15 that I refer to in paragraph 67 above. There are significant variations in the core group, which has implications on connectivity and often makes substitution at the 3-position of the bicyclic core*

unfeasible.

72. *The skilled medicinal chemist would note the repeated use of the 7-oxo-4,5,6,7-tetrahydro- 1H-pyrazolo[3,4-c]pyridine core (72 of 110 examples), the phenyl P4 proximal ring (100 of 110 examples) and the frequency of use of the piperidinone and pyridone lactams at P4 (54 and 42 of 110 examples respectively). In the P1 position, 50/110 of the substituents are methoxyphenyl, with the balance of the alternative substituents being plausible alternatives to methoxyphenyl (such as aminobenzisoxazole), synthetic intermediates or amidine prodrugs.*
73. *The skilled medicinal chemist would note that the compound of Example 18 (which is apixaban) was prepared on a much greater scale than any of the other synthesised examples. Example 18 was prepared in an amount of 3.07g, whereas the other examples were prepared in, at most, amounts of a few hundred milligrams, and in many cases only a few tens of milligrams were prepared. The skilled medicinal chemist would also note that in Example 18 a second recrystallisation was carried out. This would have been done to extract further of the compound and thereby increase the yield of the reaction. Indeed, the second recrystallisation afforded a further 0.57g of compound.*
74. *The large quantity of the compound of Example 18 (apixaban) that was prepared would indicate to the skilled medicinal chemist that Example 18 (apixaban) was of particular interest to the inventors and that they were likely making more of this compound because, having obtained good results with this compound in their initial tests, they wanted to progress the compound for further studies, such as advanced in vivo efficacy studies, and that would require greater quantities of the compound.*
75. *In prevalent practice in 2001, the few milligrams of compound that are described as the outcomes of some of the examples in the Application would have furnished sufficient compound to generate data in primary enzyme assays (factor Xa and possibly some selectivity targets such as thrombin and trypsin), plus an early efficacy measure in a blood- based anticoagulant assay (such as PT, Prothrombin Time extension) and perhaps high throughput physicochemical assays and/or in vitro DMPK predictions such as microsomal turnover and permeability.*

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[8] *Details of the synthesis and characterisation of examples 41 to 70 are not provided, so it is not clear to me whether the inventors actually made these compounds.*

Synthesis of increasingly large amounts of compound was commensurate with progression of the compound for further profiling such as in vivo DMPK. Such studies required tens or hundreds of milligrams of compound (depending on the animal species on which tests were to be run and the nature of experiments).

76. *Consumption of sometimes costly and difficult to make intermediates to make larger quantities of one compound, rather than more analogue compounds, was indicative of increased interest in that compound. An increased amount of a compound would be required for more extensive in vivo studies, such as efficacy experiments that necessarily require increasingly larger (typically gram scale) quantities of material. Increased amounts of compound produced are indicative of the progression of the compound through the drug discovery stages outlined in paragraph 19 as further time, money and resources are invested in the series and/or most promising and advanced compound(s).*
77. *I have been asked to comment whether, at the Priority Date and based on the Application and the skilled person's common general knowledge, it would have been plausible to the skilled person that apixaban was an effective (and improved, cf. paragraph 99) factor Xa inhibitor. I consider that this would have been plausible for the reasons that I give below:*

    A. *Apixaban has the P1-core-P4 structure that was common to known factor Xa inhibitors. Apixaban has neutral P1 and P4 groups and the skilled person would know that factor Xa inhibitors with neutral (or weakly basic) P1 and P4 groups were an area of particular interest (for the reasons that I give above) and that several factor Xa inhibitors with neutral or weakly basic groups had been shown to be effective as anticoagulants and in animal models.*

B. *Apixaban has a methoxyphenyl group in the P1 position. As I describe at paragraph 48 above, methoxyphenyl substituents had been shown to bind in the S1 pocket of factor Xa through modelling and inhibitors with methoxyphenyl as both P1 and P4 motifs had shown factor Xa activity.*

C. *The core of apixaban is a cyclised (or rigidified) version of the core of DPC423. The skilled person would recognise that this modification was likely to increase affinity and/or improve metabolic stability towards hydrolase enzymes. As I describe above, DPC423 had attracted particular attention as an effective, weakly basic factor Xa inhibitor. The skilled person would recognise the similarities between the structure of apixaban and that of DPC423 (which was from the same research group) and the modifications that had been made to it.*

D. *Apixaban has a lactam group in the P4 position. As I describe above at paragraph 37, the skilled person would know that the S4 binding pocket allowed for considerable variability and, having been presented with it, would consider it plausible that the lactam substituent of apixaban would bind in the S4 pocket. The skilled person would also recognise that the distal lactam in the P4 position of apixaban is a plausible isostere for the distal aromatic moiety of DPC423.*

E. *The P1 and P4 groups, the carboxamide substituent and the core of apixaban are reused many times in Application. Indeed, 32 of the compounds exemplified in the Application only have a single point (i.e. single substituent) change from apixaban. The skilled person would understand that this was because the inventors had achieved good results with these functional groups and were trying to optimise the properties of the compounds in this series by variations at other positions in the molecules.*

F. *Apixaban was synthesised on a much greater scale than any of the other examples in the Application. While many of the example compounds were synthesised in amounts that would have allowed for initial testing, such as described at paragraph 75, only Example 18 (apixaban) discloses synthesis on a scale that would allow more advanced studies to be undertaken, such as described at paragraph 76. This indicates to the skilled person that apixaban was the compound of the Application of most interest to the inventors, possibly their lead compound, and warranted progression to further studies and increased investment as discussed in paragraphs 19 and 73 to 76.The skilled person would also observe that such progression is consistent with efforts to identify a factor Xa inhibitor with the desirable pharmacological properties described in the Application*.

78. *I consider that the skilled person would find it plausible that apixaban was an effective (and improved) factor Xa inhibitor such that they would want to make and test apixaban. If the skilled person were to do so, they would find that not only was apixaban an effective factor Xa inhibitor, but that it also was an improved factor Xa inhibitor and had the other properties that were sought after in an efficacious factor Xa inhibitor.*

WO 131 AND APIXABAN

79. *WO 131 is entitled "Nitrogen containing heterobicycles as factor Xa inhibitors". Pages 1 to 2 of WO 131 set out several chemical structures which are disclosed in earlier patents and patent applications. On page 2 there is a brief description of the role of factor Xa and it is explained that inhibition of factor Xa may produce an anticoagulant effect. At the foot of page 2 it is stated that is it desirable to find efficacious and specific inhibitors of factor Xa. I note that here and elsewhere in WO 131 the text is the same as in the Application that I discuss above, although on page 2, WO 131 does not contain the list of desirable pharmacological properties that appears in the Application.*
80. *At the end of a section headed "Summary of the invention" on page 3, WO 131 explains that an object of the invention is to provide novel nitrogen containing heterobicycles that are useful as factor Xa inhibitors. Pages 3 to 15 set out a first embodiment which includes, on pages 4 to 9, a series of nitrogen containing heterobicycles with a range of possible substituents. Pages 15 to 38 set out a series of further embodiments directed to narrower classes of compounds. Embodiment 7 comprises a list of named compounds. Pages 38 to 56 set out two further broadly defined classes of compounds. Pages 63 to 96 describe various synthetic schemes for preparing the nitrogen containing heterobicycles.*
81. *Pages 96 to 206 provide details of 109 synthesised examples. These include the synthetic method and characterising data. These synthesised examples would be of most interest to the skilled person because they show the compounds that the inventors had actually made and so it is reasonable to assume that these were the compounds in which the inventors were most interested.*
82. *In a similar fashion to the analysis of the examples of the Application above, I have carried out a frequency analysis of the structural motifs in the 109 example compounds in WO 131 and this is presented below.*

[Diagram not included in judgment.]

83. *All of the synthesised examples contain nitrogen containing heterobicycles, except one exemplar that is detailed as a by-product. The examples all have the P1-core-P4 structure with which the skilled person would be familiar. However, there is a much greater diversity in the structure of the examples of WO'131 than can be seen in the examples of the Application.*
84. *35 of the 109 examples have the same pyrazolopiperidone core as apixaban. A further 35 examples contain the unsaturated 1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one core - wherein the -CH2-CH2- linker is replaced by -CH=N-. A further 20 examples include an*

extra methylene in the homologous 4,5,6,7-tetrahydropyrazolo[3,4-c]azepin-8(1H)-one structure.

85. *The most commonly used substituent at the P1 position is 3-aminobenzisoxazole which occurs in 55 of the examples. The second most commonly used P1 substituent is methoxyphenyl which occurs in 39 of the examples. All of the proximal rings in the distal position of P4 are phenyl; 62 have no additional substituents, 47 have a fluorine ortho to the point where the core is attached. The most common substituent at the distal P4 position is phenyl which occurs in 95 of the examples, with 12 imidazoles.*
86. *The most common substituent at the 3-position of the core is trifluoromethyl which occurs in 50 of the examples. The second most common is methyl which occurs in 26 of the examples.*
87. *Pages 207 to 262 of WO 131 include two tables that set out hypothetical compounds using generic structures. Pages 263 to 267 describe the utility of the compounds as useful anticoagulants for the treatment of thromboembolic disorders through inhibition of factor Xa. Much of the language in this section appears to be the same as in the Application that I discuss above.*
88. *The skilled person would recognise that WO 131 was a patent application from the research group that had developed DPC423 and would see that in WO 131 the inventors were investigating compounds that were similar to DPC423 but with a cyclised core. For example, Example 67 has the same P1, P4 and core substituents as DPC423, but with a cyclised core. The skilled person would recognise that the inventors of WO 131 were using neutral and weakly basic substituents, in line with the direction of factor Xa research that I explain at paragraphs 39 to 45 above. The skilled person would expect that most of the examples of WO 131 would be effective factor Xa inhibitors, such as Example 67, which has a similar structure to DPC423.*
89. *I have been asked to comment whether apixaban would have been obvious to the skilled person on the Priority Date based on WO 131.*
90. *None of the examples described in WO 131 has a lactam substituent at the P4 position as apixaban does. Lactams are not listed amongst the preferred P4 substituents in the preferred embodiments described in WO 131 (see e.g. the list of preferred B groups at page 28, lines 1 to 7). There is no disclosure of a lactam substituent in WO 131.*
91. *To arrive at apixaban based on WO 131, the skilled person would need to make the following choices:*
    - A. *A pyrazolopiperidone core structure has to be chosen;*
    - B. *A methoxyphenyl must be chosen for the P1 position;*
    - C. *A carboxamide must be chosen as the substituent on the core;*
    - D. *A particular lactam needs to be chosen for the P4 position.*
92. *As regards the first of these choices, WO 131 provides examples of seven different cores with the pyrazolopiperidone core exemplified as often as an unsaturated aza-analogue 1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. As regards the second choice, the methoxyphenyl group is the second most common P1 substituent used in the examples, with aminobenzisoxazole being the most comment P1 substituent.*
93. In *relation to C above, only six examples in WO 131 have a carboxamide substituent on the core, whereas 80 of the 109 examples have a trifluoromethyl or methyl substituent. Trifluoromethyl and methyl substituents are small, nonpolar groups, whereas carboxamide is a polar group. The skilled person would consider the repeated use of trifluoromethyl and methyl substituents in the examples as indicating a preference for this type of substituent and to point away from using a polar substituent such as carboxamide, which is only exemplified in combination with the 1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one core. To arrive at the lactam found in apixaban based on the Markush formula disclosed in WO 131, the following choices need to be made from within the options for substituent B (page 12, line 24 of WO 131):*

[Diagram not included in judgment.]

- A. *a 6 membered heterocyclic system must be selected amongst the range of 5-10 membered heterocyclic systems;*

B. the 6 membered heterocyclic ring must contain just one nitrogen atom;
C. the 6 membered heterocyclic ring must be connected via that single nitrogen atom;
D. of the possible R4a substituents of the 6 membered heterocyclic ring (shown below) a single carbonyl group must be selected

[Diagram not included in judgment.]

E. The carbonyl selected above must be adjacent to the nitrogen.

94. *A lactam is a theoretical example that the skilled person could derive from the broad Markush formula if they were asked to do so. However, I do not consider that the Markush formula of WO 131, or anything else in WO 131, renders the choice of a lactam substituent obvious. Nor do I consider that the examples in WO 131 would guide the skilled person towards an alicyclic compound such as piperidinone, or pyridone based on the nature of the exemplified P4 substituents.*

95. *A further difference between the Application and WO 131 that would be noted by the skilled person is that the molecular weight range of the example compounds in WO 131 is substantively distributed to much heavier compounds in comparison to apixaban (apixaban MW = 459.51 Da). The median molecular weight of compounds in WO 131 is 546 and the median in WO 652 is 486. 51 of the exemplified compounds in WO 131 have a mass >550 Da. 93 have a mass >500 Da, and just 5 are lighter than apixaban. These five examples (shown in Figure 20 below) include a brominated intermediate[9] (Example 109), whilst the other 4 examples each include a centre likely to possess moderate basicity with calculated pKa values indicating some ionisation at pH 7.4 (the imidazole of examples 10 and 105 has a predicted basic pKa of 6.93 in SciFinder, the same source predicts the dihydroimidazole of Example 75 to have a basic pKa of 8.49, whilst the amino methyl of Example 99 is predicted to be 9.40). Each structure possesses 2 or more points of differentiation from apixaban. The skilled person would note the disconnect between the molecular weights of the majority of example compounds of WO 131 and the observations of Lipinski (paragraph 41), that a lower molecular weight (of less than 500) would be desirable and indicative of likely better solubility and permeability.*

[Diagram not included in judgment.]

96. *As can be seen in Figure 21 below, overall, based on the Daylight calculated log P (CLogP) values, the structures of the examples in WO 131 are indicative of a generally higher intrinsic lipophilicity (Log of Partition Coefficient) than apixaban (Clog P = 1.89). Although the examples of WO 131 with sulphonamide and sulphone substituents are of a similar range of CLog P, that is with additional mass/heavy atoms that are necessary to achieve this modulation of lipophilicity.*

[Diagram not included in judgment.]

97. *Furthermore, many of the examples of WO 131 are basic compounds (69/109, have basic groups at the P4 position, 14/109 have basic groups at P1, with 3 overlapping) with higher intrinsic lipophilicity (log P) as illustrated in Figure 21. These compounds are likely to be protonated at physiological pH (pH 7.4) and this will markedly reduce the effective lipophilicity of these compounds (Distribution Coefficient or Log D, pertinently measured at pH 7.4).*

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[9] *The skilled person would notice that other examples could be synthesised from Example 109 – e.g. Example 105 in the manner of Example 104.*

This is a feature likely to limit the permeability of the molecules exemplified in WO 131, making them less likely to achieve sufficient absorption from the gastrointestinal tract, a prerequisite for an oral drug although it would contribute to increased solubility, in line with the comments of Zhu and Scarborough (Appendix RY16) regarding the need to achieve balanced physicochemical properties (paragraph 40 above). As I describe in the CGK section above, in order to overcome the problems associated with basic compounds, the discovery of neutral factor Xa inhibitors was a goal of those working in the field.

98. *In comparing the Application and WO 131, the skilled person would also observe that, unlike apixaban, none of the exemplified compounds in WO 131 had been synthesised in a gram scale or on a scale that suggests they were scaled up for comprehensive testing, as discussed at paragraph 76 above.*[10]

99. *For the reasons that I give above, I do not consider that apixaban would have been obvious to the skilled person based on WO 131. In addition, as I explain above, once the skilled person had been shown the structure of apixaban, the skilled person would recognise that apixaban would have improved properties, in terms of reduced weight and neutrality (and thus equalised and optimised intrinsic and effective lipophilicity), over most, if not all, of the example compounds of WO 131. Finally, unlike the Application, WO 131 does not give the skilled person any reason to believe that any of the example compounds of WO 131 had achieved sufficiently promising results that warranted progression to advanced studies that would require synthesis on a multi-gram scale. I declare that all statements made in this expert statement from. my own knowledge are true and that all statements made on information and belief are believed to be true.*

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10 *Of the examples from WO 131 where the synthesised amounts are recorded, 4 are <= 10 mg (mg= milligrams or 1/1000th of a gram; 8 are between 11 and 35 mg, 20 are between 36 and 94 mg; 11 are between 110 and 308 mg; and there is one of 500 mg. In the Application, 10 are<= 10 mg; 15 are between 11 and 35 mg; 8 are between 40 and 100 mg; 10 are between 104 and 424 mg and apixaban is at 3.07grams or 3070 mg.*

Statement #2 of 2[26]

5. *As a preliminary point, I have been advised that I should clarify that, when preparing my Expert Report for the Swedish proceedings, I was provided with the documents identified in sub-paragraphs (A) to (J) and paragraph 6 below. I was advised at the time that documents A to I were documents that the parties in the related UK proceedings had relied upon as forming part of the common general knowledge for the purpose of those proceedings. These are precisely the types of documents that the skilled medicinal chemist would consult and I agree would form part of the common general knowledge of the skilled medicinal chemist.*

    A. *Rai (2001)*
    B. *Al-Obeidi (1999)*
    C. *Pauls & Ewing (2001)*
    D. *Leung (2000)*
    E. *Light (2001)*
    F. *Maignan (2001)*
    G. *Betz (2001)*
    H. *Zhu & Scarborough (2000)*
    I. *Zhu & Scarborough (1999)*
    J. *Ries (2000)*

6. *The review article Leadley 2001 is a good summary of research on the biology of factor Xa and the rationale for the pursuit of factor Xa as a target and would form part of the common general knowledge. Document Pinto (2001) (Appendix RY13) is a disclosure of the factor Xa inhibitor DPC-423. As I say at paragraph 47 of my First Witness Statement, the publication of DPC-423 generated a lot of interest in the field.*

Reply to the Witness Statement of Dr Paul Edwards dated 14 April 2022

7. *I have been provided with a copy of the Edwards Statement and have been asked to review and comment on it. My comments as set out in this witness statement are not exhaustive; where I have not commented on a particular aspect of the Edwards Statement, this does not mean that I agree with Dr Edwards.*
8. *I agree with Dr Edwards at paragraph 5.7 where he says that a medicinal chemist would be involved in different stages in a drug development project. However, in my experience, a medicinal chemist is often involved earlier than the Hit discovery stage e.g. in helping to design/procure/synthesise assay substrates or assay standard inhibitors, designing focused libraries and/or deciding what compounds are to be put through a high throughput screen. Also, upon joining a new project, in addition to the matters described by Dr Edwards at paragraph 6.2, a medicinal chemist would apply learnings from any previous projects undertaken with similar targets or experiences with particular molecular structures or features.*
9. *I agree with paragraph 6.5 of the Edwards Statement where Dr Edwards says:* "A cell contains thousands of different types of enzyme molecules, each specific to a particular chemical reaction". *However, enzymes are not only found in cells e.g. factor Xa and the prothrombinase complex it is part of, the targets of apixaban, are extracellular, acting in the bloodstream. Also, rather than being specific to a particular reaction, some enzymes are known to have more than one function.*
10. *I would add to Dr Edwards' description at paragraph 6.7 that one of the key things about proteases is that certain features of specific active site amino acids of proteases actually facilitate the reaction by actively participating in the process.*
11. *I find Dr Edwards' comments at paragraph 6.8 and his references to lowering activation*

[26] *The papers annexed to the statement are not included.*

energy confusing – with factor Xa, not only does the active site topology stabilise the transition state and thus lower the activation energy, but also the Serine195 at the active site participates in the reaction through the formation of a transient covalent bond to the carbonyl of the S1 residue (arginine).

12. *I disagree with Dr Edwards' suggestion at paragraph 6.9 that all enzymes have a high degree of specificity. Certain enzymes are promiscuous in nature – a good example of this is the cytochrome P450 family of enzymes that metabolise many substrates. Furthermore, many hydrolase enzymes have broad synthetic utility. For clarity, I would add that not all enzymes break bonds – some enable synthetic reactions. I would also add that all naturally occurring (physiological) molecules are synthesized by enzymes.*
13. *In paragraphs 2.9 and 6.13, Dr Edwards refers to DPP-IV as a "serine protease". However, unlike factor Xa, DPP-IV is not a trypsin-like serine protease. DPP-IV is a serine exopeptidase, acting on the N-terminal end of the protein recognising and cleaving a variety of dipeptide motifs, whereas factor Xa (like trypsin) is a serine endopeptidase, acting more towards the middle of its substrate (Prothrombin).*
14. *At paragraph 6.14, Dr Edwards says that similarity in amino acid sequence of substrate structure would mean that the skilled person would be disposed to think that a compound which inhibits factor Xa "might or would" also inhibit another serine protease. I disagree that the skilled person would believe that a factor Xa inhibitor would necessarily or be likely to inhibit another serine protease. A factor Xa inhibitor is deliberately designed to inhibit factor Xa (a trypsin-like serine protease) by anchoring in the primary specificity pocket and would thus be unlikely to be recognised by very many serine proteases. The skilled person would appreciate that different inhibitors will have different specificities, that selectivity was achieved across many compounds at the Priority Date and the more heavily designed and optimised the inhibitor the less likely it would be to inhibit another serine protease. The very elements of the factor Xa inhibitor that facilitate shape complementarity and recognition with factor Xa would be more likely to not fit, or to clash, within the pockets of other, even related, proteases.*
15. *I would add to paragraph 6.15 that in the case of thromboembolic disorders it is not so much dysfunction, overexpression or hyperactivation of an enzyme but rather dysregulation of a feedback-controlled cascade/network of reactions that is damped down by modulation of particular factor in the intrinsic pathway. But not to such an extent that the cascade is unable to respond to the amplification of responses in the extrinsic pathway (in which factor Xa also plays a pivotal role) that enable local clot formation to prevent bleeding.*
16. *Arising from paragraph 6.20, I disagree with Dr Edwards that, at the Priority Date, a drug discovery team undertaking a search for any potential drug would be looking for potency, as measured by Ki, in the low nanomolar or high picomolar-level range. There are many examples of compounds that were being investigated at the time that were a lot less potent than single nanomolar Ki, including iNOS compounds with micromolar potency that I had been working on over the five years before the Priority Date,1 and indeed many marketed drugs possess activity at micromolar levels or even higher. For factor Xa, I agree that a drug discovery team at the Priority Date would have been looking for potent inhibitors, ideally in the low nanomolar range, but translation of this activity into anticoagulant efficacy was far more important.*
17. *At paragraph 6.21, it would have been understood that it is efficacy, and not potency, that would determine the dose required. I agree with Dr Edwards that higher potency can compensate for other sub-optimal properties – this was noted in Zhu & Scarborough (2000) – but it is more complicated than Dr Edwards is suggesting. A less potent drug can be more efficacious than a higher potency drug – efficacy depends on achieving the right balance of properties and pharmacology to deliver effective concentrations to the site of action.*
18. *At paragraph 6.22, Dr Edwards conflates potency with affinity when saying that* "the potential drug will need to be as potent as the natural substrate to compete for the enzyme" – *I do not think it makes sense to talk about potency of a natural substrate, as the potency of an inhibitor is a relative concept that is measured as against the behaviour of an enzyme in binding to or turning over its natural substrate or an artificial ligand or substrate. I also disagree with the final sentence of paragraph 6.22* – "The specifics of balancing these potencies would be a

matter on which the skilled pharmacologist would take the lead" – *this is something that the skilled medicinal chemist does by design, the pharmacologist would confirm the outcomes, or use their skills to balance signal versus sensitivity in setting up the assay.*

19. *At 6.23, in referring to "activity towards those plasma proteins", Dr Edwards also conflates activity with affinity – use of the former in this context suggests that the compound will possess some modulatory effect on the plasma proteins, rather than just bind (specially or non-specifically) with them. I would also say that the 10-fold shift in potency between disease relevant assays and primary biological assays described in paragraph 6.23 is understated in cases of serine protease inhibitors in anticoagulant assays.*
20. *I agree that a drug development team would be looking for selectivity of at least 100-fold. I also agree that the exact figure would be project specific, and it would also depend on the risk manifested by any other protease inhibited. For example, at the Priority Date, as well as investigating selective factor Xa inhibitors, research teams were investigating compounds that could act as dual inhibitors of both factor Xa and thrombin. This was in part based on the knowledge that warfarin, for example, acts indirectly on several proteases in the coagulation cascade, with the notion that a compound with similar broad activity but lesser drug-drug interactions compared with warfarin had potential value.*[2]
21. *I disagree with Dr Edwards where he says at paragraph 6.26* "If a drug was suitably potent against factor Xa, the skilled medicinal chemist would have an expectation that binding to other (off-target serine) proteases would likely result". *Factor Xa inhibitors that were potent tended to also be selective. This is not surprising given how different the pocket topology of factor Xa is from the vast majority of serine proteases. With other* trypsin-like *serine proteases (e.g. thrombin and plasma kallikrein) there is risk of lower selectivity due to commonalities in the S1 pocket, but selectivity was generally achieved via the S4 binding sites' interactions. As regards thrombin binding, interactions at S2 and S3 are important for thrombin potency whereas the S2 and S3 pockets are absent in factor Xa, this provided a further feature that allowed researchers to design selective factor Xa inhibitors.*
22. *Based on my experience with factor Xa, any compound we made was tested to see its effect on clotting at an earlier stage than Dr Edwards suggests at paragraph 6.27. A molecule's effects on clotting is one of the first things that is tested following demonstrable activity in the factor Xa assay, and this would occur before pharmacokinetic studies. pharmacokinetic studies.*
23. *Arising from paragraph 6.30, while I agree that it is always necessary to carry out tests, and I agree that even small chemical changes can have material effects, a medicinal chemist works to a hypothesis and would expect certain changes to have certain desired effects. The Magic Methyl Effect and similar effects are of interest precisely because they are often anomalous. Ultimately, it is necessary to carry out tests, but the skilled person is working according to a hypothesis and carries out the tests to confirm that hypothesis. I would not, however, put enantiomers in the category of compounds with "small changes" between them and I do not believe that the skilled medicinal chemist would expect enantiomers to necessarily work in the same way.*
24. *In paragraph 6.38.4, Dr Edwards presumably means to refer to a candidate with the properties to deliver an efficacious drug, rather than a commercially successful one which would be dependent on clinical outcomes and a variety of other commercial factors.*
25. *The 18 documents returned by Dr Edwards' second search – 11 of which are cited by Dr Edwards on the basis that they would be of particular interest to the skilled medicinal chemist – comprise a surprisingly small number of hits, particularly considering that factor Xa was – I believe – one of the most researched targets in the field of medicinal chemistry at the Priority Date and already was the subject of numerous monographs and reviews.*

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[2] *Nar, H. et al. Structural basis for inhibition promiscuity of dual specific thrombin and factor Xa blood coagulation inhibitors. Structure 9, 29-37, doi:10.1016/s0969-2126(00)00551-7 (2001) (Appendix RY*

Dr Edwards does not describe the parameters of his search though it has not returned a representative selection of documents that the skilled medicinal chemist would have consulted. It is also surprising that, of the 11 papers identified as being of particular interest to the skilled medicinal chemist, 4 of these are not primarily concerned with factor Xa inhibitors, but rather inhibitors of different enzymes. In summary, although Dr Edwards has identified several publications that I agree are representative of the CGK of the skilled medicinal chemist (for example Appendix 9 (Maignan), Appendix 10 (Pauls & Ewing 2001), Appendix 11 (Rai), Appendix 12 (Quan & Wexler) and Appendix 13 (Zhu & Scarborough 2001), Dr Edwards appears to have considered a relatively narrow set of publications, including several publications that I do not consider reflect CGK and indeed that do not relate to factor Xa.

26. *In addition to the companies listed by Dr Edwards in paragraph 6.43.1, there were many other pharmaceutical companies involved in factor Xa research around the Priority Date, including DuPont Pharmaceuticals, Zeneca, Millennium Pharmaceuticals, Eli Lilly, GSK,Yamanouchi, Banyu, Warner-Lambert, Hoechst-Marion-Roussell, COR. There was a huge amount of research being undertaken in respect of factor Xa at the Priority Date, as is evident from the number and diversity of companies involved in the research, and this would have been known to the skilled medicinal chemist. I believe that Dr Edward's reference to the molecule "FXV672" in that paragraph should be a reference to "FXV673", a compound which mentioned in the Pauls and Ewing (2001) paper included as Appendix 10 to his statement (and Appendix RY12).*
27. *At paragraph 6.44.4, Dr Edwards places a surprising emphasis on the similarity between the S4 pockets of factor Xa and tissue-type plasminogen activator (tPA). That similarity – they differ by only one residue – is identified in Maignan (Appendix RY10) as an exception to the statement that* "[s]electivity is often achieved by interaction with the S4 pocket since it differs significantly from most trypsin-like serine proteases". *The passage in Maignan does not, however, say that selectivity over tPA or over any other member of the trypsin-like serine protease family is a challenge, contrary to the conclusion drawn by Dr Edwards. Indeed, the factor Xa inhibitors identified by Dr Edwards as being compounds of particular interest in paragraph 6.46.2 all show good levels of selectivity over tPA.*
28. *As already described at paragraphs 14 and 21 above, I do not agree with Dr Edwards' view (e.g. as expressed at paragraph 6.45.1) that achieving selectivity for factor Xa over other serine proteases would have been considered difficult to achieve. This is evident from the selectivity achieved by factor Xa inhibitors described in the review articles that I refer to in my First Witness Statement. I am not sure what exactly Dr Edwards means by* "significant degree of homology" *but I do not believe that could be said about factor Xa and any non-trypsin-like serine protease for example. I would add that it is not just residues that differ, but also binding pocket architecture. For example, the lack of S2/S3 folds in factor Xa is particularly relevant in terms of achieving selectivity over other trypsin-like serine proteases.*
29. *At paragraph 6.46.1 and 6.46.2, Dr Edwards identifies a list of compounds of interest at the Priority Date. This list is in my opinion incomplete and not fully representative of the state of progress in factor Xa research at the Priority Date and I refer to my First Witness Statement in that regard. Dr Edwards does not, for example, discuss any of the neutral inhibitors that were a focus of research at the Priority Date as described in 38 and 39 of the First Witness Statement.*
30. *At paragraph 6.47.1, Dr Edwards states* "The most common P1 group is the benzamine, which is highly basic." *I assume that Dr Edwards means the "benzamidine" group, which was widely used and is referred to in Maignan as the most common P1 group. Although benzamidine may have been the most common P1 group its shortcomings were well documented by the Priority Date and strategies to circumvent these were emerging using less basic or neutral alternatives.*
31. *At paragraph 6.47.4, Dr Edwards reproduces a passage from a section of Maignan entitled "The Special Cases". The example referred to by Dr Edwards is described in Maignan as one of two reported classes of inhibitors that "stand aside from the other[s] by the way they bind to the active site of the protein". Thus this example is very much a structurally exceptional compound amongst factor Xa inhibitors.*
32. *Arising from paragraph 6.47.5, I agree that the central linker or scaffold connecting P1 and P4 has significant implications both for the design and synthesis of factor Xa inhibitors. Dr Edwards mentions the use of rigidified scaffolds. The importance of rigidification in terms of conformational restraint or favouring ready transitions between solution and bound conformations was well-*

documented at the Priority Date. As was the role of rigidification in ensuring minimum entropy loss on binding. Rigidification had the potential to increase the potency of a factor Xa inhibitor, if the compound was locked in the right conformation, and could also improve the entropy of binding, again increasing potency. The nature of the chemistry used to construct the central linker or scaffold could, inter alia, influence the stability of the molecule, disfavour the release of potentially problematic metabolites such as anilines, or contribute to the physicochemical properties of the molecule as a whole.

33. *I agree with Dr Edwards at paragraph 6.47.6 where he explains that modelling of factor Xa inhibitors did generally have predictive power regarding their likely binding mode at the Priority Date. This is also the conclusion of the authors of the Maignan article. As Dr Edwards mentions, and as I have described in my First Witness Statement, there were some cases where unexpected binding modes such as "reverse binding" were observed.*
34. *I agree that the skilled medicinal chemist would be aware of lactams as a general class of functional groups. I do not agree that lactams are any more commonly used in chemistry and drug design than the very large number of alternative functionalities.*
35. *I do not consider that the fact that beta-lactam groups occur in certain antibiotics would motivate the skilled person to use a delta-lactam group in an entirely different molecule designed to interact with an entirely different biological target. I would be very surprised if it was suggested to me that a lactam substituent should be used in a factor Xa inhibitor because lactam groups occurred in certain antibiotics. While these antibiotic compounds include a lactam, it is a substituted and fused beta-lactam, not the prosaically N-linked delta-lactam of apixaban. I have illustrated the different types of lactams in Figure 1 below. I do not believe that the skilled medicinal chemist would put beta-lactam antibiotics in the same category as delta-lactam substituents, as Dr Edwards implies at paragraph 7.3 – they are very different classes of compounds. Aside from the difference in size and structure, beta-lactams are very reactive whereas gamma- and delta-lactams are generally more stable.*
36. *Dr Edwards at paragraph 7.5 discusses the difficulty the skilled medicinal chemist would have in identifying where the lactam should be located, in particular for a compound to have activity against factor Xa. As explained in paragraphs 56 to 67 and 70 to 72 of my First Witness Statement, it would be apparent to the skilled medicinal chemist that the patent is concerned with compounds having a pendant lactam substituent.*
37. *I disagree with Dr Edwards' conclusions at paragraph 7.6 in so far as, as outlined my First Witness Statement, it would have been plausible to the skilled team that apixaban was an effective factor Xa inhibitor.*
38. *In respect of paragraph 7.8.2, I do not consider that the skilled medicinal chemist would find the discussion of thrombin inhibition confusing or of concern. As mentioned above, the prospect of dual thrombin and factor Xa inhibitors was still being considered at the Priority Date and some of the alternative central scaffolds described in the examples of the Application could indeed have favoured thrombin inhibition by interaction with the S2 and S3 pockets of thrombin, as I describe above.*
39. *At paragraph 7.9, while I agree that the skilled team would need to do tests – and would not know what the results would be prior to doing them – the topology (i.e. the chemical structure and arrangement of chemical groups), molecular weight and neutrality of the compound of Example 18 (apixaban), as discussed in my First Witness Statement, would impact on the skilled medicinal chemist's level of confidence that the tests would be successful and, in turn, would encourage the skilled medicinal chemist to do those tests. This is in addition to the amount of apixaban that had been synthesised in Example 18 which, as outlined in my First Witness Statement, the skilled medicinal chemist would understand as indicating that at least some of those tests had already been successfully carried out.*
40. *I disagree with Dr Edwards' conclusions at paragraph 7.13 about the skilled person not being taught anything, explicitly or implicitly, about which compounds may be preferred from within the vast array disclosed. Apart from the fact that there are a number of specific examples and what are described as preferred embodiments identified in the Application, the skilled medicinal chemist would naturally be most interested in the compounds that have actually been made. Looking at these, the skilled medicinal chemist would observe frequently occurring substituents as outlined in my First Witness Statement. As I also explain in my First Witness Statement, the skilled person would be familiar with the P1-core-P4 structure that was common to factor Xa inhibitors, and that Dr Edwards describes at paragraph 6.47. The skilled person would readily recognise this structure in the compounds of the Application,*

including apixaban, and would therefore recognise how these compounds might bind to factor Xa and which parts of these compounds would be important for binding to factor Xa.

41. *While I agree with Dr Edwards that there are no specific data in the Application as to the selectivity of the compounds disclosed, the skilled person would understand that the compounds that had been made would have also been tested and that, for apixaban at least, the inventors had likely successfully conducted tests for selectivity and as a result set out to synthesise it on a larger, multi-gram scale, notwithstanding encountering poor yields in doing so, in order to carry out more advanced testing.*

APPENDIX 17

Translation of French Judgment

S.A.S. Teva Santé v. *BMS Holdings Ireland Unlimited Company*
(Judicial Court of Paris, 8th June 2023)

PROCEEDINGS

At the hearing of 6 March 2023 held in a public hearing and partly in council chambers, in accordance with Article L. 153-1, 3° of the French Commercial Code, the information was given to lawyers that the decision would be delivered on 8 June 2023.

JUDGMENT
Handed down following proceedings held partly in council chambers pursuant to Article L. 153-1, 3° of the French Commercial Code, and publicly, subject to the requirements for the protection of trade secrets of Bristol-Myers Squibb Holdings Ireland Unlimited Company, in accordance with Article L. 153-1.4° of the French Commercial Code (paragraph 61).
In the presence of both parties
In the first instance

PRESENTATION OF THE FACTS:

1. Bristol-Myers Squibb Holding Ireland Unlimited Company (hereinafter "BMS') is a subsidiary of Bristol-Myers Squibb, which designs, develops and distributes pharmaceutical products particularly *"innovative"* medicines. BMS holds numerous patents, including the European patent designating France no. EP 1 427 415 (hereinafter EP'415) with the title "Compounds containing lactam and their derivatives as factor Xa inhibitors", and the French supplementary protection certificate no. FR11C0042 (hereinafter SPC'042) issued on the basis of this patent.
2. Patent EP'415 comes from PCT application no. WO03026652 (WO'652) of 29 September 2001. It results from the submission of a European application dated 17 September 2002 by Bristol-Mayers Squibb Company and was issued on 12 August 2009. It claims the priority of the provisional application US 60/324 165 P filed on 21 September 2001 by the inventors, Donald Pinto and Mimi Quan, employees of DuPont Pharmaceuticals Company, which became Bristol-Myers Squibb Pharma Company on 2 October 2001
3. Patent EP'415 covers useful compounds such as anticoagulant agents for treating thromboembolic disorders, particularly apixaban. The marketing authorisation (MA) for the active ingredient apixaban was granted to BMS in the European Union under no. EU/1/11/691/001 on 18 May 2011. The proprietary medicinal product covering apixaban is marketed under the name Eliquis®. This MA resulted in the submission of supplementary protection certificate application no. 11C0042, with the certificate issued by the INPI on 11 January 2013.
4. Patent EP'415 expired on 17 September 2022 while SPC'042 will expire on 20 May 2026.
5. Eliquis ® is an oral anticoagulant indicated for the prevention of thrombosis, which manifests itself with the appearance of blood clots that can cause pulmonary embolism or cardiovascular events. It has been a major advance in the prevention and treatment of this phenomenon, with a global turnover of USD 9 billion in 2020.
6. Teva Sante is the French subsidiary of the Israeli pharmaceutical group Teva, which is primarily known for its generic activities; it is responsible for the distribution in France of the products developed by the group, and in particular the generic proprietary medicinal product "Apixaban Teva" in its various dosages (2.5 mg and 5 mg). Teva Bv holds the marketing authorisation for this generic proprietary medicinal product.
7. By letter dated 5 March 2021, renewed on the following 19 April, BMS asked Teva Sante and Teva Bv to confirm that they will not commit any infringing acts, reminding them of its rights on patent EP4l5 and SPC042.

8. It is in this context, and while other disputes oppose the parties with respect to other national parts of the same patent in many other countries, that Teva Sante, by writ dated 4 October 2021, summoned Bristol-Myers Squibb Holdings Ireland Unlimited Company before the Judicial Court of Paris, for invalidity of the French part of the EP'415 basic patent and therefore, for invalidity of SPC'042.
9. On 25 March 2022, the parties entered into a participatory procedure agreement for pre-trial purposes. In accordance with their convention and pursuant to the provisions of Article 1546-1 of the French Code of Civil Procedure, the investigation was concluded on 14 February 2023 and the hearing was set on 6 March 2023.
10. In accordance with the provisions of Article 1564-4 of the French Code of Civil Procedure, the parties have, by acte d'avocats [document notified by one barrister to another through a court bailiff] of 13 February 2023, formalised their claims submitted for judgment by the Court as follows:

For Teva (conclusions no. 2 served by the virtual private network of lawyers on 30 November 2022):
DECLARES the nullity of the French part of patent EP 1 427 415 Bl for all its claims;
DECLARES the nullity of SPC FR11 C0042;
ORDERS, in application of the provisions of Article 700 of the French Code of Civil Procedure, Bristol-Myers Squibb Holdings Ireland Unlimited Company to repay TEVA SANTE for all the costs and fees that the latter had incurred to assert and defend its rights, i.e. the sum of €300,000 (three hundred thousand), subject to adjustment;
ORDERS Bristol-Myers Squibb Holdings Ireland Unlimited Company, to pay all costs which will be directly recovered by the SCP August & Debouzy and Partners. lawyers, in accordance with the provisions of Article 699 of the French Code of Civil Procedure;

For Bristol-Myers Squibb Holdings Ireland Unlimited Company (conclusions no. 3 served by RPVA (virtual private barrister network] on 30 January 2023):
Dismisses the applications for declaration of invalidity of patent no. EP 1 427 4 I 5 Bl and the supplementary protection certificate FR 11C0042 issued by Teva Sante;
Orders Teva Sante to pay Bristol-Myers Squibb Holdings Ireland Unlimited Company the sum of €300,000 under Article 700 of the French Code of Civil Procedure, subject to adjustment;
Orders Teva Sante to pay all costs and the legal fees of Mr Emmanuel Larere in accordance with Article 699 of the French Code of Civil Procedure;
In the alternative:
Order that any nullity of the French pa11 of patent no. EP 1 4 2 7 4 l 5 Bl and the supplementary protection certificate FR 11C0042 not be accompanied by the performance on a provisional basis.

REASONS FOR THE DECISION

Introductory clarification (on the note sent during deliberations)
11. ln accordance with Article 445 of the French Code of Civil Procedure, after the conclusion of the debates, the parties may not file any note in support of their comments, except at the request of the presiding judge in the cases provided for in Articles 442 and 444, or if it appears that a party deliberately hid elements likely to modify the opinion of the judges (Cass. Civ. 1st, 7 June 2005, Appeal no. 05-60.044, Bull. 2005,I, no. 241).
12. In this case, the presiding judge did not ask for any post- hearing notes.
13. In addition, the exhibits produced on 11 May 2023, in. particular Exhibit no. 2.30, submitted for the discussions by Teva Sante (testimony from Mr Scott Brown of 10 March 2023 containing the "Administrative Training Manual" of 2002 in the annex, in the Defendant's possession since 27 January 2023, as well as, above all, that the chain of e-mails concerning the filing of patents made by the entity of Wilmington, ex-DuPont, which employed the inventors), confirms that Bristol-Mayers Squibb Pharma Company had no real patent autonomy, since its employees questioned the name they had to use on the patent applications, seemingly doubting that patents could belong to an entity other than Bristol-Mayer Squibb Company (see David J. Ropper's e-mail translation: *"There is a lot of confusion here in Wilmington regarding the use of the name Bristol-Mayer Squibb Pharma Company. (..) Here is what we understand about the use of the BMS Pharma name: (..) Inventions.from Wilimington's scientists must be attributed to BMS and not BMS Pharma"*, which is affirmatively answered on 23 January 2022, while the administrative training manual issued in June

provides the correction that *"the DuPont Pharmaceutical Company (DPC) records claiming a priority earlier than 10/1/2001 must be under the name of Bristol-Mayers Squibb Pharma Company. (...) You will need to change the registration cover page to indicate Bristol-Mayers Squibb Pharma Company because the form says Bristol-Mayers Squibb Company"*[2]*)*

14 *Therefore, the exhibits produced during the deliberations do not appear to be likely to modify the opinion of the Court as to whether or not BMS Company is a successor in title within the meaning of the Convention de l'Union de Paris [Paris Union Convention]. Since no disloyalty has been identified, the note sent to the Court by Teva on 11 May 2023 was therefore dismissed from the proceedings.*

1) Presentation of patent EP 1 427 415

15. According to paragraph [0001] of the description, the invention relates to compounds containing lactam and their derivatives that are trypsin- like serine protease enzyme inhibitors, in particular factor Xa inhibitors, used as anti-coagulant agents for treating thromboembolic disorders.

16. The description then mentions different prior art documents showing coagulation factor inhibitors, including factor Xa inhibitors, and in particular Document WO 131 (para. [0007]).

17. In paragraph [0018], it is specified that activated factor Xa, the main practical role of which is the generation of thrombin by the limited proteolysis of prothrombin, occupies a central position that links the intrinsic and extrinsic activation mechanisms in the common final blood coagulation process. (Hereinafter extracted from the conclusions of Teva illustrating the *"coagulation cascade").*

[Diagram not included in judgment.]

18 Thrombin generation, the latest serine protease in the fibrin clot generation pathway from its precursor, is amplified by the formation of the prothrombinase complex (factor Xa, factor V, Ca2+ and phospholipid). As it is calculated that a factor Xa molecule can generate 138 thrombin molecules (Elodi, S., Varadi, K.: Optimisation of the conditions of the catalytic effect of factor IXa-factor VIII complex: Likely role of the complex in the amplification of blood clotting. Thromb. Res. 1979, 15, 617-629), factor Xa inhibition may be more effective than thrombin inactivation in interrupting the blood clotting system.

19. [0019] Therefore, effective and specific factor Xa inhibitors are needed as potentially valuable therapeutic agents for treating thromboembolic disorders. It is therefore desirable to discover new factor Xa inhibitors and, in particular, new compounds with improved pharmacological characteristics compared to known factor Xa inhibitors. For example, it is preferable to find new compounds with improved factor Xa inhibitory activity advantageous features in one or more of the following categories, but are not limited to:

(a) pharmaceutical properties (e.g. solubility, permeability and the possibility of prolonged release formulations);
(b) dosage requirements (e.g. lower dosages and/or single daily dosing);
(c) factors that decrease peak blood concentration characteristics (e.g. clearance and/or volume of distribution);
(d) factors that increase the concentration of the active drug at the receptor (for example, protein binding, volume of distribution);
(e) factors that decrease the risk of drug-drug clinical interactions (e.g., inhibition or induction of cytochrome P450 enzyme);
(f) factors that decrease the potential for undesirable side effects (e.g., pharmacological selectivity among serine proteases, potential chemical or metabolic reactivity, and limited penetration within the central nervous system).

20. Paragraph [0028] of the description then discloses apixaban in the form of a compound represented by the formula (I) (below) or a pharmaceutically acceptable salt.

[Diagram not included in judgment.]

[2] *The emphasis was not added by the Court*

21. Paragraphs [00114] to [00117] then describe the in vitro and in vivo tests that can be performed to measure

the efficacy of the compounds of the invention as factor Xa inhibitors. In this respect, the description specifies that efficacy is determined using purified human factor Xa and a synthetic substrate. The hydrolysis level of factor Xa of the chromogenic substrate S2222 (Diapharma/Chromogenix, West Chester, OH) is measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate leads to the release of pNA, which is monitored spectrophotometrically by measuring the increase in absorbance at 405 nm. A reduction in the rate of absorbance change at 405 nm in the presence of the inhibitor is indicative of enzyme inhibition. The results of this test are expressed as an inhibitory constant, Ki.

22. [00115] Factor Xa dosages were performed in a 0.10 M sodium phosphate buffer, pH 7.5 containing 0.20 M of NaCl and 0.5% of PEG 8000. The constant of Michaelis, Km, for hydrolysis of the substrate was determined at 25°C using the Lineweaver and 15 Burk method. Ki values were determined by leaving 0.2-0.5 nM of human factor Xa (Enzyme Research Laboratories, South Bend, IN) react with the substrate (0.20 m M - I m M) in the presence of an inhibitor. The reactions lasted for 30 minutes and the speeds (speed of absorbance change over time) were measured between 25 and 30 minutes. 25-30 minutes. The following relationship was used to calculate Ki values: where vo is the control speed in the absence of an inhibitor; vs is the rate in the presence of the inhibitor; 25 I is the inhibitor concentration; Ki is the dissociation constant of the enzyme-inhibitor complex; S is the substrate concentration; Km is the Michaelis constant.

23. [00116] The compounds tested in the above trial are considered to be active if they present a Ki=10 μM. The preferred compounds of the present invention have Ki of S 1 μM. More preferred compounds of the present invention have Ki=0.1μM . Even more preferred compounds of the present invention have Ki=0.01μM. Still even more preferred compounds of the present invention have Ki= 0.001 μM.

24. [00117] The antithrombotic effect of the compounds of the present invention can he demonstrated in a rabbit arteriovenous (AV) thrombosis model. In this model, rabbits weighing 2 to 3 kg anaesthetised with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tube containing a piece of silk wire. Blood will flow from the femoral artery through the AV shunt into the femoral vein. Exposure to the flowing blood of 10 silk fibre will induce the formation of a significant blood clot. 40 minutes later, the shunt is disconnected and the silk fibre coated with a blood clot is weighed. Test agents or excipient should be given (intravenously intraperitoneally. subcutaneously or orally) before opening the AV shunt. Percent inhibition of thrombus formation is determined for each treatment group. Values of ID 50 (doses that cause 50% inhibition of thrombus formation) arc calculated by linear regression.

25. Paragraph [00180) specifies that, in the following examples, Example 18 is an example of the present invention, while the other examples are provided as reference examples.

26. Example 18 is described as follows in paragraphs [00246] to [00251]: 1-(4-Methoxyphenyl)-7-ox.o-6-[4-(2-oxo- 1-piperidinyl) phenyl-4, 5,6,7-tetrahydro-1H pyrazolo[3,4-c] pyridine-3-carboxamide. This is apixaban.

27. [00246) Part A. of 4-iodoaniline (45.82 g, 209.2 mmol) and triethylamine (65.61 mL, 470.7 mmol) are dissolved in THF (800 mL) and cooled to 0°C. 5-5 bromovaleryl chloride (50.0 g, 251.1 mmol) dissolved in THF (200 mL) is added drop by drop to the reaction. The reaction was warmed to ambient temperature and stirred overnight. The reaction was cooled to 0°C and potassium tert-butoxide(70.43 g, 627.6 mmol) was added slowly. The reaction was warmed to ambient temperature and stirred overnight. The reaction was concentrated, redissolved in ethyl acetate (500 mL) and 3N HC1 10 (500 mL), extracted with ethyl acetate (2 x 250 mL), washed with HC1 IN (3 x 250 mL), washed with brine (l x 250 mL) and dried (Na2SO4). Purification by silica gel chromatography using a gradient of 0% to 100% of ethyl acetate/hexane as eluent to afford 51.03 g (81%): NMR 1H (CDC13) d 7.70 (d,j = 8.4 Hz, 2H), 7.03 (d,j= 8.8 Hz, 2H), 3.62(t, j 5.9 Hz, 2H), 2.56 (t, j = 5.7 Hz, 2H), 2.50 to 1.88 (m. 15 4H)ppm.

28. [00247] Part B. The above Part A intermediate lactam (85.17 g, 282.8 mmol) and phosphorus pentachloride (205.91 g, 990.0 mmol) were dissolved in HCC13 (750 mL) and brought to reflux for 3½ h. The reaction was poured over ice and then quenched further with water, extracted with CHC 13 (3 x 400 mL), washed with brine 20 (1 x·400 mL). dried (MgSO4) and concentrated. This residue was dissolved in morpholine (400 mL) and refluxed overnight. Reaction was concentrated and purified by silica gel chromatography using a 0% to 100% gradient of ethyl acetate/hexane as eluent to afford 68 g (63%): NMR 1H (CDC13) d 7.68 (d,j=8.8 Hz,2H),7.11 (d,j=8.8 Hz,2H), 5.66 (t,j=4.8Hz,1H), 3.82 (t,j=4.8Hz,4H), 3.77 (t,25 j= 6.8Hz, 2H),2.89 (t,j = 4.8 Hz, 4H), 2.53-2.47 (m, 2H) ppm.

29. [002481 Part C. To p-anisidine (16 g, 0.129 mol) in conc. HCI. (40 ml) and water (100 mL) at 0°C, was

slowly added sodium nitrite (9.4 g, 0.136 mol) to water (60 mL). The reaction was stirred cold for 0.5 h. To the above reaction was poured a mixture of chloroacetoacetate (22 g, 0.133 mol), ethanol (100mL), sodium acetate (32 g, 0.389 mmol) and 30 water (400 mL). The reaction was stirred for 2 hours at ambient temperature. The precipitate was filtered-off and dried to afford the hydrazone as a red gum (30.3 g, 91%): NMR 1H (CDC13) d 8.28 (s, 1H), 7.18 (d,j= 9.1 Hz,2H), 6.90 (d,j =9.2Hz, 2H), 4.41 (q,j = 8 Hz, 2H), 3.80 (s, 3H), 1.42 (t,j = 6.9Hz, 3H) ppm.

30. [00249] Part D. To the hydrazone from Part C (0.7 g, 2.7 mmol) and the morpholine compound 35 from Part B (0.7 g, l .8mol) in toluene (25 mL), was added triethylamine (2 mL, 14.2 mmol) and the reaction was heated to reflux for 6 h. The reaction was cooled to room temperature and water was added. The mixture was extracted with ethyl acetate. washed with water, IN HCl, saturated NaHCO3 solution and dried (Na2SO4). Purification on silica gel using 3:2 hexanes/ethyl acetate afforded a morpholine intermediate that was dissolved in CH2C12 (50 mL) and TFA (2 m L). After 24 h, the reaction was diluted with CH2C12, washed with water and saturated NaHCO3 solution and dried (Na2SO4) to afford 0.17 g (18%) foam: NMR 1H (CDC13) d 7.70 (d,j =0 8.5 Hz, 2H), 7.47 (d, j = 9.1 Hz, 2H), 7.09 (d, j =8.8 Hz, 2H), 6.93 (d, j = 9.2 Hz, 2H), 4.49 (q,j=6.9 Hz, 2H), 4.12 (t,j - 6.5 Hz, 2H), 3.81 (s, 3H), 3.34 (t, j=6.6 Hz, 2H). 1.45 (t, j = 6.9 Hz. 3H) ppm; Mass Spec ESI (M+H)·+ 517.9.

31. [002501 Part E. To iodo compound from Part D (25 g, 0.048mol), was added valerolactam (6.7 g, 0.067 mol), K2CO3 (8 g, 0.058 mol), degassed DMSO (100 mL) and CuI (1.84 g, 0.009 mol). The reaction was heated to 130 °C for 24 h. The reaction was cooled, partitioned with EtOAc/H2O, extracted and dried (MgSO4). Purification by silica gel chromatography using 0 to 10% MeOH/CH2C12 as eluent afforded 155 g (21%),) 1-(4-methoxyphenyl)-7-oxo-6[4-(2-oxo-l- piperidinyl)phenyl]-4,5,6,7-tetrahydro 1 H-pyrazolo[3,4-c]pyridine-3- carboxylated ethyl as a tan foam; NMR 1H (CDC 13) d 7.49 (d, j = 9.2 Hz,2H), 7.35 (d,j = 8.8 Hz, 2H), 7.26 (d,j = 8.1 Hz, 2H). 6.92 (d,j= 8.8 Hz, 2H), 4.49 (q, j = 7.3 Hz, 2H), 4.13 (t, j =6.6 Hz, 2H, 3.81 (s,3H), 3.59 (m, 2H), 3.39 (t,j = 6.6 Hz, 2H), 2.55 (m, 2H), 1.91 (m, 4H), 1 .45 (t, j = 7.3 Hz, 3H) ppm.

32. [00251] Pa11 F. To ester from Part E (4.8 g, 0.009 mol) was added 5% NH3 in ethylene glycol (40 m **L)** and the mixture was heated to 120 °C for 4 h in sealed vessel. Water was added and the resulting solid was collected. Purification by silica gel chromatography using 0 to 10% MeOH/CH2C 12 as eluent afforded 3.5g of a white solid. A portion of the solid was recrystallized from CH2C12/EtOAc to 25 afford 2.5 g of the title compound. The remaining solid and filtrate material was recrystallized in isopropyl alcohol to afford an additional 0.57 g for a total of 3.07 g (68%): NMR lH (CDCI3) d 7.49 (d,j = 8.8 Hz, 2H),7.37 (d,j=9.1 Hz, 2H), 7.26 (d,j = 8.8 Hz, 2H), 6.98 (s, lH) 6.95 (d,j = 9.2 Hz, 2H), 6.28 (s, 1H), 4.14 (t,j = 6.6 Hz, 2H), 3.81 (s, 3H), 3.61(m, 2H), 3.39 (t,j = 6.6 Hz, 2H), 2.63 (t,j=6.2 Hz, 2H), 1.96 (m, 4H)ppm.

33. Patent EP'4 I 5 consists of the following 29 claims:.

1.Compound represented by the formula (1) or a pharmaceutically acceptable salt thereof:

[Diagram not included in judgment.]

2. A compound according to claim 1, which is represented by the formula (1).

3. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of the formula (1) of claim 1 or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition, comprising: the pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 2.

5.Compound of claim 1 or 2 for use in a therapy.

6. Pharmaceutical composition according to claim 3 or 4 for use in a therapy.

7. A compound of claim 1 or 2 for use in treating a thromboembolic disorder. .

8. A pharmaceutical composition of claim 3 or 4 for use in treating a thromboembolic disorder.

9.Use of a compound of claim 1 or 2 in the manufacture of a medicinal product for use in treating a thromboembolic disorder.

10. Use of a pharmaceutical composition of claim 3 or 4 in the manufacture of a medicinal product for use in treating a thromboembolic disorder.

11.A compound for use in treating a thromboembolic disorder according to claim 7 or use of a compound according to claim 9, where the thromboembolic disorder is selected from the group consisting of arterial

cardiovascular thromboembolic disorders, ·venous cardiovascular thromboembolic disorders and thromboembolic disorders in the chambers of the heart.
12.A compound for use in treating a thromboembolic disorder according to claim 7 or use of a compound according to claim 9, where the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, 5 transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e)) haemodialysis or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.
13.A compound for use in treating a thromboembolic disorder according to claim 12 or use of a compound according to claim 12, wherein the thromboembolic disorder is an acute coronary syndrome.
14. A compound for use in treating a thromboembolic disorder according to claim 12 or use of a compound according to claim 12, where the thromboembolic disorder is ischemic sudden death, transient ischemic attack or stroke.
15. A compound for use in treating a thromboembolic disorder according to claim 12 or use of a compound according to claim 12, where the thromboembolic disorder is deep vein thrombosis.
16.A compound for use in treating a thromboembolic disorder according to claim 12 or use of a compound according to claim 12, wherein the thromboembolic disorder is pulmonary embolism.
17. A pharmaceutical composition for use in treating a thromboembolic disorder according to claim 8 or use of a pharmaceutical composition according to claim 10, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders and thromboembolic disorders in the chambers of the heart.
18.A pharmaceutical composition for use in treating a thromboembolic disorder according to claim 8 or use of a pharmaceutical composition according to claim 10, where the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (C) stents, (d) cardiopulmonary bypass, (e) haemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.
19. A pharmaceutical composition for use in treating a thromboembolic disorder according to claim 18 or use of a pharmaceutical composition according to claim 18, wherein the thromboembolic disorder is an acute coronary syndrome.
20. A pharmaceutical composition for use in treating a thromboembolic disorder according to claim 18 or use of a pharmaceutical composition according to claim 18, where the thromboembolic disorder is ischemic sudden death, transient ischemic attack or stroke.
21. A pharmaceutical composition for use in treating a thromboembolic disorder according to claim 18 or use of a pha1maceutical composition according to claim 18, wherein the thromboembolic disorder is a deep vein thrombosis.
22. A pharmaceutical composition for use in treating thromboembolic disorder according to claim 18 or use of a pharmaceutical composition according to claim 18, wherein the thromboembolic disorder is pulmonary embolism.
23. A compound and a second therapeutic agent, for use in treating a thrombolytic disorder, where the compound is a compound of claim 2 and the second therapeutic agent is at least one agent selected from a second factor Xa inhibitor, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibition agent, a thrombolytic agent and a fibrinolytic agent.
24.Use of a compound and a second therapeutic agent in the manufacture of a medicinal product for use in treating a thrombolytic disorder, wherein the compound is a compound of claim 2 and the second therapeutic agent is at least one agent selected from a second factor Xa inhibitor, an anti-coagulant agent, an antiplatelet agent, a thrombin inhibition agent, a thrombolytic agent and a fibrinolytic agent.
25.A compound and a second therapeutic agent, for use in treating a thrombolytic disorder according to

claim 23 or use of a compound and a second therapeutic agent of claim 24, wherein the second therapeutic agent is at least one agent selected from warfarin, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatroban, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam,diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, disulfatohirudine, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase and streptokinase.
26.A compound and a second therapeutic agent, for use in treating a thrombolytic disorder according to claim 23 or use of a compound and a second therapeutic agent of claim 24, where the second therapeutic agent is at least one anti-platelet agent.
27.A compound and a second therapeutic agent, for use in treating a thrombolytic disorder according to claim 26 or use of a compound and a second therapeutic agent of claim 26, wherein the second therapeutic agent is at least one of aspirin and clopidogrel.
28. A compound and a second therapeutic agent, for use in treating a thrombolytic disorder according to claim 27 or use of a compound and a second therapeutic agent of claim 27, where the anti-platelet agent is clopidogrel.
29.A compound and a second therapeutic agent, for use in treating a thrombolytic disorder, according to claim 27 or use of a compound and a second therapeutic agent according to claim 27, where the anti-platelet agent is aspirin.

2) On the lack of any inventive step (claims 1 to 4)

Pleadings of the parties

34. Teva Sante argues that, in order to be inventive, a patent must make a true contribution to the state of the art in the form of a verifiable technical effect demonstrated by its own documentation. It adds that this contribution cannot be demonstrated by the use of external documents and in partiuclar after the filing or priority date. It argues that doctrine and case law are unequivocal in this regard.

35. Teva Sante, in essence, argues that BMS was not in possession of the invention on the priority date, which in turn results from the review of application W0'652, which does not provide any technical evidence rendering *"plausible"* or *"credible"* that this patent provides a solution to the technical problem posed (improved treatment of thromboembolic disorders by factor Xa inhibition), whereas, if BMS was in possession of the invention, the patent would still be annulled because failure to disclose the results of its tests demonstrating that it was in possession of the invention constitutes, according to Teva Sante, a violation of the social pact, as such disclosure is the counterpart of the monopoly.

36. In support of its application for cancellation, Teva Sante argues that nothing in the application WO'652 demonstrates that BMS was in possession of the invention (apixaban), which was never actually claimed and had only been the subject of any publications demonstrating its technical effect from 2007, i.e. 6 years after the filing of the priority document. Teva Sante emphasises that patent WO'652 describes the synthesis of 140 different compounds, and that as of the date of its filing, the researchers could only hope that one of these 140 compounds would be more promising than the others, without having specially identified apixaban by that date. Teva recalls in this respect that it is at the request of the examiner that BMS selected apixaban from the multitude of compounds described and claimed in the initial application. In addition, it states, the description of patent EP'415 mentions that the compounds identified are strong thrombin inhibitors (in addition to factor Xa); this has been revealed to be false and, in its opinion, demonstrates that BMS only discovered the actual technical effect of apixaban after the submission. Similarly, the only parameter cited in the application is the Ki inhibitory constant, but in such a wide range ($\leq$10 µM) that no therapeutic conclusion can be drawn from it. Finally, the person skilled in the art could not draw any conclusions from the quantities of product synthesised in Example 18, and, in particular, that in the spirit of the inventors, it had the best pharmacological qualities.

37. In any event and invoking the known elements of Decision G2/21 as of the date of closure, Teva Sante argues that here, the person skilled in the art could have serious doubts about the fact that the applicant was in possession of an invention, so that the Court must refuse to examine the evidence outside the documentation

of the patent provided by BMS in connection with this dispute, which it also indicates that it is not exhaustive. It underlines anyway that, in its certificate, Dr Pinto even states that he had considered apixaban as an *"early applicant"* only in March 2002 i.e. after the priority date.

38. Teva Sante concludes in the same way that there is no inventive step for patent EP'415, because a person skilled in the art would have succeeded in the invention by combining the teachings of Document WO' 13 l, which discloses that radical B can be a lactam group, through routine work on the screening of molecules all disclosed in this document. Teva Sante also invokes the combination of Documents WO'l31 and WO'919.

39. Bristol-Myers Squibb Holdings Ireland Unlimited Company seeks rejection of the invalidity claim alleging lack of inventive step of patent EP'4l5.

40. First of all, it recalls that, contrary to the claims of Teva Sante,-French case law never required the patentees that they demonstrate, through testing or disclosure of data, in the patent, the claimed technical effect, except in the case of patents referred to as second therapeutic application, for the purpose that they are considered sufficiently described, as it is the same (new) function of the product that constitutes the invention. •

41. BMS adds that apart from this very specific hypothesis, French case law sanctions by nullity, lack of inventive step or for insufficient disclosure, depending on the case, patents that do not contribute to the state of the art, this, without having ever laid down as a condition (additional to those of the EPC or the French Intellectual Property Code) that the patent should contain the results of tests demonstrating the claimed technical effect, evidence of such a technical effect at the date of filing or priority which can be reported by any means by the patentee, the case law admitting evidence after the filing on a case-by- case basis.

42. BMS recalls that the invention has as its starting point the high affinity (therefore a weak Ki) of bicyclic pyrazoles with factor Xa that led to the filing of patent WO'l3l and the launch of clinical trials (Example 61 of this patent was even considered to be “early candidate appointment”). The clinical trials conducted with the compounds identified in patent WO'131 nevertheless revealed their very high toxicity. The common point identified was that all toxicities manifested in tissues or organs, resulting in the idea in Dr Pinto's team of researchers, and this is the starting point of the research that led to the invention, to develop a compound with a low volume of distribution (Vd), for it to remain in blood plasma and diffuse less into tissues and organs, while for the product to remain in blood plasma for as long as possible (long half-life or Tl/2), the compound had to have low clearance (Cl). This is how multiple compounds were identified and tested and, among them, compounds comprising a lactam in position P4, showed high affinity with factor Xa (low Ki), including apixaban in January 2001. In vitro studies conducted in January 2001 have shown that apixaban (which is a compound comprising: in the central position, a bicyclic pyrazole, dihydropyrazolopyridinone, in position P4, a 2-oxo-1-piperidinyl lactam group and a phenyl group, and in position P1, a p-methoxyphenyl group as well as a carboxamide group, had a very low Ki, and so was a potent factor Xa inhibitor. In vivo studies conducted in May 2001 subsequently showed that it had the desired pharmacokinetic properties, namely low clearance and a low volume of distribution, leading to a long half-life. Tests conducted in July 2001 in larger animals confirmed apixaban's good results. Application WO'652 was then extended to a European level at the end of this series of tests.

43. BMS further specifies that the description indicates that the compounds *"even more preferred"* had a Ki ≤0.001 µM, and paragraph [0180] distinguishes Example 18 (which corresponds to apixaban) as the invention, with other examples provided for reference. Similarly, a person skilled in the art would have understood, when reading the description and Example 18, that apixaban was prepared in larger quantities (it is the only one made in grams) and that it would be used for both in vitro and in vivo testing. BMS adds that it was during the examination procedure, in 2008, that it limited its claims to apixaban (the application originally claimed protection of 74 compounds including apixaban) and demonstrated the low Ki of its Example 18 compared to the compounds in Document WO'131.

44. BMS challenges the speculative nature of Patent EP'415. It argues that there can be no serious doubt that it was in possession of the invention on the priority date and in any event, offers to demonstrate, using

laboratory notebooks and reports from its researchers (confidential documents) as well as Dr Pinto's certification, that tests showed prior to September 2001, the high affinity of apixaban with factor Xa and its strong pharmacokinetic properties. BMS also recalls that European patent law does not know a *"best mode requirement"* condition that would require it to describe the best operating procedure of the invention.

45. Finally, BMS argues that the person skilled in the art would not have succeeded in the invention only by means of Document WO'l31, without implementing a research program, to identify possible bicyclic compounds, not including all possible substitutes, or billions of different compounds, while this document does not even put it on the pathway for the desired pharmacokinetic properties (Vd, Cl and Tl/2). It adds that Teva Sante only achieves the formula of a compound similar to apixaban through that document because it makes an arbitrary selection from passages without ties between them and because it knows about the invention. This is therefore a subsequent reasoning that the court will not be able to follow under any circumstances. The same shall apply for the combination of Document WO'131 with patent WO'919 (which shows an oxazolidinone, having a central monocycle structure, with a lactam group in position P4) which would not have led a person skilled in the art to apixaban in anyway, being unable to find any incentive in these documents.

Court assessment

a - On the *"ab inilio plausibility"* (or the need to publish from the filing or priority date of proof of the technical effect claimed)

46. In accordance with Article L. 614-12, paragraph 1 of the French Intellectual Property Code, the nullity of the European patent is pronounced for France by a court decision for any of the reasons referred to in Article 138 (1) of the Munich Convention. Under Article 138 (1) of the Convention, the European patent may be declared invalid, with .effect for a Contracting State, only if: (a) the subject matter of the European patent is not patentable under A1ticles 52 to 57 (...). It is also the result of Articles 52 (1) and 56 of the Convention that European patents are granted for any invention in all technological fields, provided that it is new, involves an inventive step and is susceptible of industrial application; an invention shall be considered to involve an inventive step if, for a person skilled in the art, it does not arise in an obvious way from the state of the art.

47. The person skilled in the art, on the identification of which the parties have no divergence of views, is the one from the technical field where the problem arises that the invention, the subject of the patent, proposes to resolve (Cass. Com., 20 November 2012, Appeal no.11-18.440). The purpose of Patent EP'415 is to propose new compounds with improved pharmacological and pharmacokinetic characteristics compared to known factor Xa inhibitors, acting as anticoagulants. The result is that the person skilled in the art is in this case a multidisciplinary team consisting of a medicinal chemist, a pharmacologist, a pharmacokineticist, and a physician experienced in anticoagulants. The parties do not object to the content of the general knowledge of the person skilled in the art.

48. As further rightly recalled by BMS, French case law does not require the patentees to demonstrate, through testing or disclosure of data that would appear in the patent, the claimed technical effect, except in the case of patents referred to as second therapeutic application.

49. In this case, the invention relating to the new therapeutic application of a known product, it is expected of the patentee to describe through tests, in particular, this new effect claimed, for the purpose that the person skilled in the art understands the invention and that the invention is viewed as *"plausible"* (and sufficiently described): *"Where a claim relates to a subsequent therapeutic application of a substance or composition, obtaining that therapeutic effect is a.functional technical characteristic of the claim, so that if, in order to meet the requirement of sufficency of disclosure, it is not necessary to clinically demonstrate this therapeutic effect, however; the patent application must directly and unambiguous y reflect the therapeutic application claimed, so that the person skilled in the art understands, based on commonly accepted models, that the results reflect this therapeutic application."* (Cass. Com, 6 December 2017, Appeal no. 15-19.726, Bull. 2017, IV, no. 160)

50. This requirement does not exist for other patents that normally cover a new product regardless of its therapeutic application (which is the case here of claims 1 to 6). •

51. However, case law does not consider as valid a patent which, from the point of view of the person skilled in the art, would not make any contribution to the state of the art or which would allow its applicant to reserve a field of research that has not yet made concrete and technical results. An invention must therefore have a *"credible"* or *"plausible"* technical effect at the filing date, the absence of which is sanctioned in the ground of lack of inventive step (see for example TGI Paris, 6 October 2009, RG no. 07/16446, Teva/Sepracor). The credible nature of the technical effect is assessed at the priority or filing date (e.g. TGI Paris, 6 October 2009, RG no. 07/16446, Teva/Sepracor), in view of the elements contained in the application, including the patent claims, without the latter being obliged to provide the results of tests or trials or any other data (see for example CA Paris, 29 October 2020, RG no. 126/2019, Ethypharm/Merck Sharp & Dohme Corp). Post-filing elements may also be considered but cannot be used as a single basis for demonstrating credibility of the technical effect (e.g. TGI Paris, 6 October 2009, RG no. 07/16446, Teva/Sepracor).

52. In this case, it is constant that the initial application contained neither paragraph [00028], nor paragraph [00180], mentioned above, which were added during the examination phase in 2008, i.e. well after the priority date; the claims were similarly fully recast: they initially claimed the protection of a very large number of compounds (74) according to the possible variants of the different substitutes around the central structure.

53. It may be inferred that the applicant was not in possession of the invention at the time of filing and filed an idea or intuition.

54. The Court notes, however, that the initial filing specifically discloses apixaban (page 76 of the translation of Document WO'652), which is further exemplified (no. 18), admittedly among 140 examples and a description of over 100 product summaries.

55. However, the Court notes that this Document WO'652 reveals tests, resulting in the determination of the *"most preferred"* compounds with very high affinity and in particular Ki ≤0.001 µM. This Document WO'652 further specifies that the invention relates to a factor Xa inhibitor whose pharmacological and pharmacokinetic properties are improved. It further describes that 3.07 g of apixaban have been synthesized (page 178). This quantity undoubtedly distinguishes apixaban among all the examples of synthesised compounds, in that it is, by far, the largest quantity synthesized by the description (no other example falls to the gram, with the other largest quantity synthesized being Example 91: 0.34 g).

56. A person skilled in the art would have necessarily deduced, on the basis of common general knowledge, that the patentee thought that apixaban was a promising compound, or even the most promising compound[3].

57. Of course, this conclusion is not formally expressed in the description from the priority date and is further less corroborated by data made public in this document when it was filed.

58. However, such a requirement for disclosure of results does not appear in the EPC, neither in the implementing regulation, nor in French case law for a patent other than a second therapeutic application (for it to be sufficiently described), whereas in this case, the extent of patent EP'415 monopoly corresponds to apixaban (regardless of its therapeutic application).

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[3] It is also the conclusion that he English decision reached (items 171 and 172 of the High Court of England and Wales judgment of 7 April 2022. *"The 3g point is not completely without relevance (...) it sets apixaban apart form the other exemplified compounds based on information in '652 itself that I think the skilled reader would notice. However (...) I do not see how the point can go any further than the patent thought that apixaban was promising"*).

59. As it has been seen, the technical effect of apixaban is also credible from the point of view of a person skilled in the art when reading the patent specification as filed (it being noted that the protection of third parties is in principle ensured through the complaint of undue extension). As a result, it does not appear to be justified here to deprive BMS from the possibility of providing proof of the contribution of this compound to the state of the art, on the date of filing, by the production of external and contemporary elements.

60. In this case, BMS submits to the proceedings the laboratory notebooks and reports of its researchers, prior to the filing of the WO'652 application, which indisputably demonstrate in a manner that has actually not seriously been disputed, that it was in possession of the invention, i.e. a factor Xa inhibitor, useful in treating thromboembolic disorders, with improved pharmacological and pharmacokinetic properties.

61. In particular, the tests conducted with compound AG0023 (apixaban) show an excellent Ki of 0.08 µ M (results of the 18 January 2001 test: confidential Gide exhibit no. 5.3), a low clearance in dogs (Cl: 0.02 Llfulkg), as well as a low volume of distribution (0.2Lkg) with the conclusion that (redacted)

62. These elements fully confirm the research program as outlined by BMS (see 42 above and Gide exhibit 5.1) and the discovery by Dr Pinto and his apixaban colleagues before the priority date.

63. The plea based on the lack of *"plausibility" or "credibility"* of a contribution of patent EP'4 l 5 to the state of the art at the time of its filing, and therefore lack of inventive step of claims 1 to 4, is therefore rejected. •

B - On the lack of inventive step with regard to Document WO'131 taken alone or in combination with Document WO'9 l 9

64. The elements of the prior art are destructive of inventive step only if, taken alone or associated with each other in a combination reasonably accessible to the person skilled in the art, they made it possible for the latter to bring the same solution to the problem resolved by the invention.

65. Document WO'131 undeniably corresponds to the state of the art closest to the invention. This is a patent from DuPont Pharmaceuticals Company and was also the starting point of Dr Pinto and his colleagues. The WO'131 application therefore teaches the use of compounds whose central structure consists of two merged cycles containing nitrogen and, in a paragraph [3] (page 22 of the document in English) the following central (invariable) G structure (among 34 possible structures):

[Diagram not included in judgment]

which serves as a starting point for Teva to consider that a person skilled in the art would dhave managed, from this document, by selecting the preferred variables it shows, in its opinion, a "*molecule screening*" routine work.

66. However, if apixaban potentially corresponds to one of the possible compounds with this structure as a starting point, Teva does not explain why it chooses this structure, other than because it knows about apixaban. This company continued with an arbitrary selection of substitutes among those possible, particularly with regard to lactam group (which corresponds precisely to the •discovery of Dr Pinto and his colleagues), as the choice of an oxo-piperidinyl group is not taught at any time by patent WO'13 I, and even less in position P4.

67. That is why Teva Sante ultimately argues that a person skilled in the art would have succeeded the invention by combining the teachings of the WO'131 application with patent WO'919 which discloses a compound no. 129 (over 254) containing a 2-oxo-l-piperidinyl lactam grouping: (see below extract from BMS conclusions, page 74, in which the lactam group is circled in red).

[Diagram not included in judgment]

68. However, once again, the argument by Teva is based on an arbitrary selection of substitutes resulting from their knowledge of the invention and not from demonstrating an incentive for the person skilled in the art, as the compounds containing a 2-oxo-1-piperidinyl lactam grouping of Document WO'919 are not even presented in this document as being preferred. As the reasons for favouring this lactam grouping are not exposed, the combination of Documents WO'131 and WO'919 therefore does not appear to be reasonably accessible to the person skilled in the art.

69. The argument based on the lack of inventive step of claims 1 to 4 of the French part of patent EP'415 is therefore rejected.

3) On the lack of novelty (claims 1 to 6)

Pleadings of the parties

70. Teva Sante argues that BMS cannot validly avail itself of its priority date (21 September 200 I), so that the new Document WO'681 (which is a Bristol-Myers Squibb patent claiming a priority date of 10 December 2001) which shows a compound 62 that corresponds to apixaban, is enforceable on the grounds of novelty.

71. Teva Sante recalls that the U.S. interim application US' 165 was filed by two U.S. inventors, employees of DuPont Pharmaceuticals Company, whose assets have been transferred to Bristol Myers Squibb Pharma Holding, which will become Bristol Myers Squibb Pha1ma Company, to which both inventors will assign their invention on 3 November 2001. However, the PCT application was filed on 17 September 2002 by a separate entity, Bristol Myers Squibb Company, while the priority right will only be subject to a transfer agreement (from Bristol-Myers Squibb Pharma Company to Bristol Myers Squibb Company) on 23 April 2007. Teva Sante deducts from this chronology that the PCT application was filed by a person who could not benefit from the right of priority, which is therefore not validly claimed.

72. Teva Sante argues that it is perfectly admissible to raise this plea, since case law and doctrine are univocal to consider that the right to claim a priority can be challenged by any interested person when the patent has been granted, as the effect of this dispute is not necessarily the nullity of the patent but the displacement of its effective date. Teva Sante relies primarily on the EPC, subsidiarity on US federal law, and infinitely subsidiarily on the law of the State of Delaware, which, according to Teva, does not allow confusion of legal persons as it would allow a mother to file a patent by claiming her daughter's right of priority.

73. Bristol-Myers Squibb Holdings Ireland Unlimited Company claims that Bristol-Myers Squibb Company cannot be validly challenged by Teva in accordance with the EPC and in accordance with French law (Cass. Com., 14 February 2012). In addition, BMS argues that the notion of successor in title must be assessed in accordance with the applicable national law, here the state law of Delaware, which knows the notion of *"effective ownership",* as opposed to the *"legal title",* applicable to situations such as that which occurred between Bristol- Myers Squibb Pharma Company and Bristol-Myers Squibb Company, the first being the wholely-owned subsidiary of the second and the two entities sharing a single patent policy, which allowed the latter to file the application.

Court assessment

74. In accordance with Article 87 (I) of the EPC, anyone who was duly filed, in or for
a) a State party to the Paris Convention for the Protection of lndustrial Property or (b) a member of the World Trade Organisation, a patent application, utility model or utility certificate, or its successor in title, enjoys, in order to file a European patent application for the same invention, a priority right for a period of twelve months from the date of filing of the first application.

75. Pursuant to Article 4 (A) of the Paris Convention for the Protection of Industrial Property, l) Any person who has regularly filed an application for a patent, a utility model, an industrial design, a trademark, in one of the

countries of the Union, or its successor in title, shall enjoy, for the purpose of filing in the other countries, a right of priority during the periods hereinafter fixed.
2) Any filing that is equivalent to a regular national filing under the domestic legislation of any country of the Union or under bilateral or multilateral treaties concluded between countries of the Union shall be recognised as giving rise to the right of priority.
3.) By a regular national filing is meant any filing that is adequate to establish the date on which the application was filed in the country concerned, whatever may be the subsequent fate of the application.

76. BMS first invokes the solution adopted with regard to the invalidity action based on lack of right to the title: *"The provisions of Article 138 para. 1(e) of the Convention on the European Patent to protect the private interests of the real owner of the patent or its* successor in title, *their infringement is sanctioned by a relative nullity which can only he invoked by the injured persons. As a result, it is inadmissible to act in nullity of a patent, a company that only supports an invention of employees whose right to the patent belongs to the employer."* (Cass. Com., 14 February 2012, Appeal no. 11-14.288, Bull. 2012, IV, no. 36)

77 However, this original solution, in that it is contrary to the provisions of Article 31 of the French Code of Civil Procedure, which reserves the possibility of determining the actions reserved to certain persons to law[4]• is in no way transposable here, as the dispute of the validity of the right of priority does not aim to protect an injured person in contrast to the invalidity of the action due to a lack of right to the title. The cause of inadmissibility put forward by BMS shall be rejected.

78 The question here is whether Bristol-Myers Squibb Company can be seen as the successors in title of the inventors, Donald Pinto and Mimi Quan, employees of DuPont Pharmaceuticals Company, which became Bristol-Myers Squibb Pharma Company, within the meaning of Articles 87 (1) of the EPC and 4 (A) of the aforementioned Paris Union Convention.

79 The determination of this quality does not fall within the scope of the EPC, which does not provide any information that would enable us to determine what this concept covers, but the national law applicable to the transmission of law, and in this case the law of the state of Delaware (where the two companies are registered), as well as the declaration of Professor Chisum citing decision Enovsys Lie vs. Nextel Commc'ns Inc., 614 F3d 1333,1342 (Fed. Cir. *2010),* although, as it raises, the question of whether a patent is valid and infringed is subject to the U.S. federal (and non-state) courts.

80. It is also consistent that under paragraph 2 of section 261 of Title 35 of the US Code, assignments of patents and patent applications must be the subject of a written statement: *"Applications for patent, patents, or any interest therein, shall be assignable in law by an instrument in writing. The applicant, patentee, or his assigns or legal representatives may in like manner grant and convey an exclusive right under his application for patent, or patents, to the whole or any specified part of the United States."*

81. It is equally constant that the state law of Delaware has a strict principle of separation of legal entities between a holding company and a daughter company, its corollary, the limitation of liability being a strong incentive for the creation of companies and investment in them (according to the testimony of Judge Holland of 29 June 2021, point 22, Gide exhibit no. 9.2).

82. It shall be deducted that the assignment of the WO'652 application, which was contained in the assets of BMS Pharma, would, in principle, have been transferred in writing between 3 November 2001 (date on which the inventors transferred their invention to BMS Pharma) and on 17 September 2002, date of filing of the PCT application, to BMS Company, so that the first (BMS Pharma) can be considered to have caused the second (BMS Company) within the meaning of the Paris Union Convention so that the second can be seen as having validly exercised the right of priority.

[4] The French legislator has not made the choice to reserve this action for nullity to the injured party, in contrast to German and English rights for example.

83. However, Judge Holland nuanced this *"binary"* conclusion on the strict distinction of companies, stating that in certain cases, the law of Delaware makes it possible to *"lift the corporate veil"* (item 25 of the certificate of 29 June 2021 mentioned above). In this respect, he underlines that the English courts were able to mitigate the rigour of the approach of requiring in all cases a written statement of the assignment prior to filing in another country (as adopted by the EPO, he said, what is confirmed by the testimony from Mrs Kinkeldey provided by Teva Sante), recognising that a patent applicant may be successor in title within the meaning of the Paris Convention under *"effective ownership",* as in the case of Fujifilm Kyowa Kirin Biologies Company Ltd. vs. ABB Life Biotechnology Ltd. [2017] EWHC 395, at points [16] (item no. 20).

84. Approving and supplementing the testimony of Judge Holland, Judge Chandler confirms the existence of the distinction, in the law of the state of the Delaware. between the legal title and the effective ownership. In an additional testimony of 26 January 2023, intended to counter the attestation of Judge Steel produced by Teva, Judge Chandler details the case law in favour of the distinction between the legal title and the beneficial ownership. In this respect, the Hollinger case is recalled, which can be transposed to the present situation:

[French text in source followed by English translation below] "18. As shown in Hollinge1; as well as in sections of the Delaware Code like Sections 220 and 271, Delaware law recognises that a parent corporation has the legal and equitable right to exercise control over and direct its subsidiaries and their assets and that a subsidiary must acquiesce in that properly-exercised control. Appyling those principles, the Mathias Statement and Golian Statement make clear that BMS Co, as 100% owner of BMS Pharma, directed and controlled BMS Pharma's intellectual property assets and that BMS Pharma followed BMS Co's directives with respect to those assets. Accordingly, I reaffirm my agreement with Justice Holland's conclusion that BMS Co had the right to cause its wholly-owned subsidiary, BMS Pharma, to assign to BMS Co the right to claim priority from the first-filed patent application, as matter of its control over a wholly-owned subsidiary.": Gide exhibit no. 9.7)

85. If the comparison with an infringement action is not fully relevant, this case law nevertheless shows that the Delaware law intends to prevent non-interesting third parties, to benefit from the fact that an assignment would not have been made in writing and to oppose non-compliance with this formality to the person who, in fact and in accordance with national law, was the real owner of the patent. As BMS rightly recalls, if this national legislation could not be taken into account by the effect of strict formalism that the Paris Union Convention does not know, the purpose of the said Convention, of which the signatories decided not to define the concept of successor in title, would not be achieved.

86. In this case, it is established that BMS Pharma was a 100% subsidiary of BMS Company, and that the management of its patent portfolio (evaluation, filing, renewal, licensing, etc.) was entirely decided by BMS Company in its sole interest (see certificate from Mrs Maria Mathias, Head of Patent Litigation of BMS Company until November 2001: *"one of my main activities was to oversee the integration of Bristol-Myers Squibb Pharma Company patent registration and renewal systems in BMS. This was a considerable workload. My goal was to put everything in place before my departure, in order to enable an effective outbreak. We did not take any steps to transfer to BMS the legal title of patents and patent applications held by Bristol-Myers Squibb Pharma Company. It was obvious that we had to leave them where they were because we had access to it anyway, so why make the effort to transfer them? It was not necessary to transfer the legal title, and there would have been no sense to do so, because BMS could in fact treat Bristol-Myers Squibb Pharma Company as a reservoir in which the intellectual properly titles it held on the date of acquisition could be hacked if necessary or otherwise affected."* Gide exhibit no. 9.4). The transfer of the legal title was hereby endorsed by an act of 23 April 2007.

87. It shall be deducted that BMS Company holds the effective ownership of patent WO'652 as of October 2001 and as such entitled BMS Pharma, so that it has validly filed this application, and validly claimed the priority right attached to the application US'165.

88. Document WO'68 l cannot therefore be examined in support of the challenge of the novelty of claims 1 to 6 of the French part of patent EP'415. This cause of nullity is therefore rejected.

4) Insufficiency of disclosure (claims 7 to 29)

Pleadings of the parties

89. Teva Sante invokes the case law of the French Supreme Court in respect of second therapeutic application. It argues that this case law is intended to apply whenever a therapeutic effect is claimed, which is the case for claims 7 to 29. The patent specification does not contain any data that would demonstrate any technical effect of apixaban. As a result, it is insufficiently described.

90. Bristol-Myers Squibb Holdings Ireland Unlimited Company recalls that neither the law nor case law requires the presence of tests in the application to consider the invention as sufficiently described, with the exception of second therapeutic applications patents. It adds that regardless of the fate of claims 1 to 6. apixaban was at the date of its filing a new product, and that the description gives the person skilled in the art the fulI means of reproducing the invention.

Court assessment

91. In accordance with Article 138 (1) (b) of the Convention of 5 October 1973 on the grant of European patents, the European patent may be declared null and void, with effect for a Contracting State, only if: (b) the European patent does not expose the invention in a sufficiently clear and complete manner so that a person skilled in the art can carry it out. It is also recalled that Article 83 of the Convention stipulates that the invention must be set out in the European patent application in a sufficiently clear and complete manner so that a person skilled in the art can carry it out.

92. These provisions are constantly interpreted in the sense that an invention is sufficiently described when the person skilled in the art is in a position to read the description and thanks to his normal professional knowledge, theoretical and practical, to carry out the invention (Cass. Com., 23 March 2005, Appeal no. 03-16.532; Cass. Com., 20 March 2007, Appeal no. 05-12.626, Bull. 2007, IV, no. 89; Cass. Com., 13 November 2013, Appeals no. 12-14.803 and 12- 15.449).

93. The patent leaflet indeed describes at length, pages 138 and 139, the process used to synthesize apixaban, so that the person skilled in the art is perfectly able to reproduce the invention. This person understands that the invention relates in particular to apixaban, an identified and exemplified compound, of which they understand that they are the most promising compound to treat thromboembolic disorders, regardless of the lack of publication of test results in the patent.

94. The cause of nullity of claims 7 to 29 of the French part of patent EP'415 based on their insufficient description is therefore rejected.

95. SPC no. 11C0042, which is not otherwise criticised other than from the perspective of the nullity of the basic patent, is therefore valid.

96. As the losing party within the meaning of Article 696 of the French Code of Civil Procedure, Teva Sante will be sentenced to the costs, as well as to pay Bristol-Myers Squibb Holdings Ireland Unlimited Company the sum of €200,000 by application of the provisions of Article 700 of the French Code of Civil Procedure.

97. As no circumstance provides otherwise, it should be recalled that this decision shall be automatically provisionally executed in accordance with the provisions of Article 514 of the French Code of Civil Procedure.

FOR THESE REASONS,

The Court, ruling in the presence of both parties, after proceedings held in part in the council chambers pursuant to Article L. 153-1, 3° *of the French Commercial Code, and by public announcement, subject to the requirements for the protection of business secrets of Bristol-Myers Squibb Holdings Ireland Unlimited Company, in accordance with Article L. 153-1,* 4° *of the French Commercial Code,*

DISMISSES the post-hearing note submitted to the Court on 11 May 2023 by Teva Sante;

DISMISSES the nullity claim against patent no. EP 1 427 415 from Bristol- Myers Squibb Holdings Ireland Unlimited Company, submitted by Teva Sante, as well as the subsequent one, for the purpose of cancelling SPC no. 11C0042;

ORDERS Teva Sante to pay the costs and authorises Mr Emmanuel Larere, lawyer, to recover those which he would have incurred and for which funds had not been provided, in accordance with the provisions of Article 699 of the French Code of Civil Procedure;

ORDERS Teva Sante to pay Bristol-Myers Squibb Holdings Ireland Unlimited Company the sum of €200,000 by application of the provisions of A1ticle 700 of the French Code of Civil Procedure;

RECALLS that this Decision is provisionally enforceable.

Handed down in Paris on 8 June 2023.

THE CLERK THE PRESIDING JUDGE

APPENDIX 18

Translation of Norwegian Judgment

Teva Norway AS and Anor v. *BMS Holdings Ireland Unlimited Company*,
Oslo District Court, 22nd May 2023

JUDGMENT

The case concerns the validity of Norwegian patent NO 328 558 B1 and supplementary protection certificate SPC/NO 2011021, as well as a claim for a negative declaratory judgment.

The parties to the case

The claimants, Teva Pharmaceutical Industries Ltd. and Teva Norway AS (hereinafter jointly referred to as"Teva") are the parent company and a subsidiary, respectively, of the global Teva Group. The group is the world's largest pharmaceuticals company by volume. In addition to generic pharmaceuticals, the group develops medicines in several therapeutic areas.

The defendant, Bristol-Myers Squibb Holdings Ireland Unlimited Company (hereinafter referred to as "BMS") is part of the Bristol-Myers Squibb group. BMS is an innovative pharmaceuticals company, which develops and sells pharmaceuticals in areas such as oncology, haematology and cardiology.

The patent and the patent history
BMS is the patent proprietor of NO 328 558 B1 ("NO 558" or the "patent in suit") and SPC/NO 2011021 ("SPC/NO 021"), which protect the product apixaban and pharmaceutically acceptable salts thereof. Apixaban is the active substance of BMS's medicinal product Eliquis.

Apixaban inhibits the natural coagulation process in the blood and prevents the formation of blood clots by reducing the blood's ability to coagulate. Hence, the medicinal product Eliquis is an anticoagulant (blood thinner).

NO 558 corresponds to European patent EP 1 427 415 ("EP 415"). The patent application was filed in Norway on 19 March 2004, and was a continuation of an international PCT application filed on 17 September 2002, published as WO2003/026652 (the "patent application" or "WO 652"). The application claimed priority from US 324 165, which was filed on 21 September 2001. There is agreement that NO 558 has priority from the said date.

BMS was granted the Norwegian patent on 22 March 2010. The patent expired on 17 September 2022. Supplementary protection certificate SPC/NO 021 protects the active substance apixaban, and pharmaceutically acceptable salts thereof, until 20 May 2026.

Blood clots, the blood coagulation process and factor Xa

In healthy persons, the function of the blood coagulation process is to limit and stop bleeding. Blood composition abnormalities, or human intervention, such as surgery, may cause blood coagulation to occur by mistake, or in the wrong part of the body. A blood clot (thrombus) may then be formed. Thrombosis occurs when blood clots in veins or arteries obstruct the blood flow. When a blood clot breaks loose and travels through the body with the blood flow, this can have serious, life-threatening consequences.

A blood clot is comprised of two main parts: platelets and fibrin. Platelets react to damage to a blood vessel and help to reduce the bleeding by clumping together in the affected site. Fibrin reinforces the clumping of platelets. Fibrin is produced through the coagulation cascade.

The coagulation cascade is a complex biological process involving numerous interacting enzymatic reactions. The enzymes involved in the coagulation cascade are referred to as □factors□, with Roman numerals being used to designate these as factors I-XIII. The addition of □a□ to the name of a factor indicates that factor in its active form. The figure below (Figure 1) provides an overview of the various pathways in the blood coagulation cascade.

[Diagram not included in judgment]

On the priority date of NO 558, it was well known that thrombotic/thromboembolic disorders could be treated by reducing blood clot formation through inhibiting the coagulation cascade. Several factors in the coagulation cascade were a potential target for an anticoagulant medicinal product.

For several decades, vitamin K antagonists, such as Warfarin, were the only oral anticoagulants used. Vitamin K antagonists only have an indirect anticoagulant effect and their use entails major disadvantages.

In the mid-1990s, factor Xa was discovered as a new and promising target for an oral drug that could prevent the formation of blood clots. Medicinal products that inhibit coagulation, by acting directly on enzymes in the coagulation cascade, are referred to as direct-acting anticoagulants.

A number of companies therefore launched research programmes aimed at developing potential factor Xa inhibitors.

Details on apixaban and the patent in suit; NO 558

NO 558 is directed to the active substance apixaban and pharmaceutically acceptable salts thereof.

Apixaban is an anticoagulant for the treatment of thromboembolic disorders. Apixaban inhibits the action of factor Xa, which, as mentioned above, is an enzyme in the so-called coagulation cascade.

Apixaban was authorised for medicinal use in the EU in May 2011. The first Norwegian marketing authorisation for Eliquis was granted by the Norwegian Medicines Agency on 18 May 2011.

The patent (Factual Bundle, hereinafter referred to as "FB" page 249) is entitled:

"*Lactam-containing compounds, pharmaceutical compositions containing the same, such compounds for use in therapy, as well as the use thereof in the manufacture of medicaments for the treatment of disorders*".

Claim 1 (FB page 486) is worded as follows:

Compound, characterised in that it is represented by formula (I):

[Diagram not included in judgment]

or a pharmaceutically acceptable salt thereof.

The field of the invention is described as follows in the introductory part of the patent:

"*The present invention relates generally to lactam-containing compounds and derivatives thereof which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical preparations containing the same, and methods of using the same as anticoagulant agents for treatment of thromboembolic disorders*" (page 1, lines 1-6, FB page 250)

The patent includes 140 embodiments, 110 of which are made in the laboratory. Example 18 is this production of 3.07 grams of apixaban(page 154, FB 403).

Chemical Background

Enzymes and proteases

Enzymes are proteins that catalyse chemical processes in living organisms. The substance on which an enzyme is acting is called the enzyme's substrate Enzymes have a three dimensional structure that allows them to bind the substrate in a specific pocket, called the "active site", where the relevant catalysing reaction takes place. The chemical transformation that occurs depends on the enzyme and the substrate. For proteases the substrate is a protein that cleaves the substrate into two parts, called the product, which readily detaches from the enzyme (Figure 2).

[Diagram not included in judgment]

Factor Xa belongs to a group of enzymes called serine proteases. Proteases have on their active sites a number of specificity pockets (S1, S2 S3, S4) to which the P1 and P4 groups of the substrate bind (Figure 3).

[Diagram not included in judgment]

Medicinal substances usually have a structure that fits into the same pocket as the substrate (Figure4). They act as inhibitors by thereby blocking the enzyme from binding its natural substrate and catalysing the reaction Selective medicinal products are only well suited for the active site of the enzyme to be inhibited. In other words, selectivity is how well a medicinal product acts on different receptors.

[Diagram not included in judgment]

The crystal structures of factor Xa, bound to different inbhitiors, show that the key binding pockets for small molecules that bind to factor Xa are S1 and S4. The various parts of the inhibitors in the case are labelled accordingly, depending on which pockets the enzyme is intended to bind, with P1 and P4 being the key ones for strong binding.

Consequently, the initial goal when developing medicinal products is to find substances that fit so well into the picket that they can bind very tightly. The substance should not be able to bind into the active site of similar enzymes or bind to other proteins. If the compound inhibits another enzyme, unwanted side

effects may occur.

IC_{50} and K_i are measures of enzyme inhibitor potency (FB page 3109). When measuring how effectively a substance inhibits an enzyme, one often determines what concentration of the substance reduces the catalytic activity of the enzyme by 50%. This is referred to as IC_{50} (inhibitory concentration). Another commonly used measure is K_i, the dissociation constant of the enzyme- inhibitor complex, K_i can be calculated from IC_{50} data if additional data are available from the method used for the measurements. The lower the K_i and IC_{50}, the more effective/potent is an inhibitor. A selective substance provides no, or very little, inhibiton of the activity of other enzymes.

Medicinal product development

The first step in medicinal product development is to identify substances that have a functional effect on the protein ("target") against which a medicinal product is to be developed. At the beginning of a project, the substances came from large- scale testing of a library of chemical substances, referred to as "high-throughput screening" (HTS), or via synthesis of structurual analogues of chemical substances that have a known effect on the target. These substances are often already available in scientific papers or can be designed based on knowledge of the properties or function of the protein. The substances undergo various tests to determine whether these have the right properties. Early in a project, the substances often do not have sufficient potency, or lack other properties required for a medicinal product.

A "lead compound" is a substance that meets the minimum requirements for a substance that is suitable as a starting point for optimising the properties considered critical for the medicinal product to be developed.

When optimising a medicinal product, an understanding of the relationship between the chemical structure of a molecule and its biological activity (structure-activity relationship ("SAR") will be gained. The use of SAR is an important method for narrowing down the choice of substances to be synthesised. Based on the available SAR, a series of substances with carefully considered structural differences are synthesised. The substances are thereafter tested to establish which changes serve to improve the drug-like properties of the substances. This process, known as "DMTA" (design-make-test-analyse), is repeated until a chemical compound with good drug-like properties has been produced. As the substances become better and better, increasingly sophisticated tests are carried out. The tests are first carried out on isolated enzymes and in cell cultures (in vitro). The more promising compounds then undergo animal experiments (in vivo). If there are no adverse results, the most promising substances are tested on humans. Almost all substances tested are rejected before reaching clinical trials, and only a small number of the substances synthesised end up as a medicinal product.

As far as factor Xa inhibitors are concerned, many compounds had been published prior to the priority date of the patent application in the case, both in the scientific literature and in patent applications from several companies. Initially, it was most important to measure the effect of the compounds on the catalytic ability of factor Xa to convert prothrombin to thrombin. Later on, the selectivity of substances for factor Xa was tested by comparing their effect on other serine proteases, how these are distributed in the body, how long the substance can be detected in the body and how quickly it is metabolised (cleared from the body). Animal studies are important to determine both the efficacy of the substances as anticoagulants and any toxic side effects.

Procedural history

Teva filed its Writ of Summons in the case on 9 June 2022, moving for patent NO 558 and SPC/NO 021 to be invalidated.

In addition, Teva has moved for a negative declaratory judgment to the effect that commercial exploitation of medicinal products containing the active substance apixaban cannot be prohibited on the basis of BMS's patent rights.

The Court notes, in this context, that the Norwegian Medicines Agency granted two marketing authorisations to Teva GmbH, which is another company in the Teva Group, on 30 October 2020. The marketing authorisations are for the products Apixaban Teva 2.5 mg film-coated tablets and Apixaban Teva 5 mg film- coated tablets (hereinafter jointly referred to as "Apixaban Teva"). Apixaban Teva is a generic copy of Eliquis.

BMS filed its Response on 9 September 2022, moving for the Court to find in its favour

The main hearing in the case was conducted over seven days during the period from 30 January to 8 February 2023. Five expert witnesses called by the parties rendered testimony. The evidence presented is noted in the court record. The Court had appointed two expert lay judges, at the request of both parties.

At the conclusion of the main hearing, counsel stated that they would inform the Court in the event of the ruling of the Enlarged Board of Appeal ("EBoA") of the European Patent Office ("EPO") in Case G 2/21 being handed down before the Court delivered its judgment in the present case. The EBoA ruling was handed down on 23 April [sic] 2023. By e-mail to the Court on 24 March 2023, the parties jointly requested that the Court set a deadline of 14 April 2023 for submitting comments on the said ruling and its implications for the present case. The parties were thereafter granted a deadline of 14 April 2023, as requested, for submitting their comments. Both parties have submitted comments on the EBoA ruling, most recently by pleadings of 24 and 27 April 2023, respectively.

By a pleading of 4 May 2023, Teva gave notice that the Court of Appeal had delivered its judgment in the appeal proceedings in the parallel invalidity action in the United Kingdom. The Court thereafter granted the parties a deadline of 8 and 9 May, respectively, for submitting any comments on that ruling. Both parties have submitted brief comments on the said ruling, as well as updated legal cost specifications.

This judgment has not been delivered by the statutory deadline. This is due to the case having been comprehensive in scope and having raised complex issues, as well as delivery of the judgment having been delayed because of the EBoA ruling of 23 March 2023 and thereafter the Court of Appeals ruling in the United Kingdom on 4 May 2023.

<u>The grounds invoked by Teva in support of its claims</u>

- NO 558 is invalid because the inventive step requirement is not met, cf. Section 52, Sub-section 1, No. 1, as read in conjunction with Section 2, of the Patents Act.

- It was not plausible that the technical problem purportedly solved by the application has actually been solved.

- The technical team, when assessing the application on the basis of common general knowledge in the art, would not consider it plausible that the large number of compounds encompassed by application WO 652, including the compound 1-{4- methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl) phenyl-4,5,6,7-tetrahydro-lH-pyrazole-[3,4-c]pyridine-3-carboxamide, which was later named apixaban, were effective factor Xa inhibitors.

Neither activity nor selectivity for factor Xa is plausibly substantiated for the compounds in the application. Consequently, the technical team would, on the basis of patent application WO 652 as read on the basis of common general knowledge in the art, be in serious doubt as to whether the problem has actually been solved.

- The technical problem must therefore be reformulated as providing alternative chemical compounds without any technical effect being plausible. It is not an invention to draw up new chemical compounds without substantiating that the claimed technical effect is plausible.

- It is furthermore argued, as an alternative approach, that the patent is invalid because the requirement that the invention must be susceptible of industrial application is not met, cf. Section 52, Sub-section 1, No. 1, of the Patents Act. The assessment called for in relation to these two grounds of invalidity is concurrent in scope and may be summarised as a plausibility requirement.

- Alternatively, it is argued that NO 558 does not meet the inventive step requirement as there is no technical contribution in relation to WO 131. When it is not plausible that WO 652 makes a technical contribution as at the application date, measured in relation to common general knowledge in the art, it is even clearer that there is no such contribution when assessed in relation to WO 131.

- In any event, the patent lacks inventive step over WO 131, as an arbitrary selection from the compounds shown in the said publication has been made without any plausible demonstration in the application of any technical contribution or improved technical effect compared to WO 131.

- As a further alternative, it is argued that the amendment during the processing of the application, whereby protection was limited to the compound apixaban, is unlawful. This is because a selection was made which could not be directly and unambiguously derived from the application as filed.

- The supplementary protection certificate is invalid because the basic patent is invalid. In any event, the supplementary protection certificate is invalid since apixaban is not protected by a basic patent in force.

- As NO 558 and SPC/NO 021 are invalid, these do not constitute grounds for prohibition of any pharmaceutical preparation comprising the active substance apixaban.

- With regard to the EPO Enlarged Board of Appeal ruling in Case 2/21, BMS has in summary argued as follows in its pleading of 14 April 2023:

  > That there is, according to the ruling in Case G 2/21, no independent requirement for plausibility in order for the inventive step requirement to be met, and that there also is no exception to the principle of free evaluation of evidence in respect of post-published evidence. The issue of whether a patent applicant or proprietor may rely on post-published evidence to substantiate a technical effect achieved by the invention, is solely a matter of whether the person skilled in the art would have derived from the patent application, having common general knowledge in mind, that the claimed effect is embodied by the invention and is encompassed by its technical teaching. There is no basis for imposing any stricter requirement.

  That the ruling in Case G 2/21 confirms that Teva's arguments are based on an incorrect standard of assessment and that post-published evidence may be taken into account in this case to support

the use disclosed in the description and the technical advance represented by apixaban.

Teva's statement of claim

1. Norwegian patent NO 328 558 B1 to be invalidated.

2. Norwegian supplementary protection certificate SPC 2011021 to be invalidated.

3. The Court to declare that producing, offering for sale, bringing to the market or using a pharmaceutical preparation containing the active substance apixaban does not constitute grounds for prohibition pursuant to Section 56a of the Patents Act, on the basis of Norwegian patent NO 338 558 B1 or Norwegian supplementary protection certificate SPC/NO 2011021.

4. Bristol-Myers Squibb Holdings Ireland Unlimited Company to be ordered to pay the legal costs of Teva Pharmaceutical Industries Ltd. and Teva Norway AS.

The grounds invoked by BMS in support of its claims

- Patent NO 558 is valid. The invention protected by the patent; the active substance apixaban, which forms part of BMS s medicinal product Eliquis, is a direct-acting factor Xa inhibitor, which represents a significant advance in the prevention and treatment of thrombi (blood clots).

- The invention meets the industrial application requirement, cf. Section 1, Sub-section 1, of the Patents Act. The use of apixaban as an active substance in medicinal products for the prevention and treatment of thrombi is disclosed in the application, and has subsequently been documented through preclinical studies and clinical trials.

  It is not required that efficacy and safety are documented in the patent application in the form of biological data. The general rule in Norwegian law is that the patent authorities accept the applicant's information on the therapeutic effect of the medicinal product, unless there are special reasons for doubting that information. If there are special grounds for doubting the information in the application, the patent applicant may substantiate the efficacy through post- published evidence. The Norwegian Industrial Property Office did not question the efficacy of apixaban during its processing of the application.
- In any event, the efficacy is substantiated by preclinical data and results from clinical trials available in the case.

- The invention also meets the inventive step requirement in Section 2, Sub-section 1, cf. Sub-section 2, of the Patents Act.

- The inventive step requirement is met when the invention was not obvious to the skilled person. In this case, the skilled person is a team with knowledge of factor Xa inhibitors and expertise in medicinal chemistry, pharmacology, pharmacokinetics, safety and clinical trials.

- The issue of whether an invention was obvious is assessed, according to established practice, by applying the problem-solution approach, which consists of three stages.

- In the first stage, it is determined which publication represents the closest prior art, i.e. the publication

that would have constituted the most promising starting point for a development leading to the invention. The parties agree that WO 131 should be considered the closest prior art.

- In the second stage, the objective technical problem solved by the invention is formulated. In this case, the problem was to provide an effective factor Xa inhibitor for the treatment of thromboembolic disorders, with improved properties. This is disclosed in the patent description, and has subsequently been documented through comparative data, where the efficacy of apixaban is compared with the most structurally similar compounds in WO 131, and is further substantiated by preclinical data and clinical trial results. There is no basis for disregarding these data, as argued by Teva.

- It is permissible to substantiate the effect through post-published evidence. Any requirement that the skilled person would as at the application date have considered the effect to be plausible based on the information in the patent application and common general knowledge in the art is in any event met.

  In the third stage, it is considered whether the solution to the problem was obvious to the skilled person, starting from the closest prior art. It is undisputed that the solution was not obvious if the problem is formulated as stated by BMS.

- The patent has inventive step over WO 131. Apixaban is not an arbitrary selection that does not represent a technical contribution beyond WO 131. Apixaban is an advance compared to the structurally most similar compounds in WO 131. Apixaban is a pioneering invention that meets the inventive step requirement by a good margin.

- The application has not been unlawfully amended. The patent applicant is entitled to amend the patent application during the processing of the application, provided that the amendment does not entail an extension of the subject-matter of the application in violation of Section 13 of the Patents Act, cf. Section 20 of the Patent Regulations. In this case, the subject-matter of the application is curtailed, in that the general formula in the original Patent Claim 1 has been replaced by a formula that only encompasses the compound apixaban, or a pharmaceutically acceptable salt thereof. Apixaban could be directly and unambiguously derived from the application as filed, in that apixaban was explicitly disclosed in Example 18 and Patent Claim 8.

- Supplementary protection certificate SPC/NO 021 is valid. SPC/NO 021 cannot be invalidated pursuant to Article 15(1)(c), as there is no basis for invalidating basic patent NO 558. Nor can SPC/NO 021 be invalidated pursuant to Article 15(1)(a), cf. Article 3(a). This is because apixaban was protected by a basic patent (NO 588) that was in force on the SPC/NO 021 application date, which was 26 September 2011.

- As NO 558 and SPC/NO 021 are valid, the exploitation of Apixaban Teva would infringe BMS□s patent rights. Consequently, the Court must find in favour of BMS with regard to Teva's claim for a declaratory judgment to the effect that the exploitation of Apixaban Teva would not constitute grounds for prohibition on the basis of SPC/NO 021 or NO 558.

- With regard to the EPO Enlarged Board of Appeal ruling in Case 2/21, Teva has in summary argued as follows in its pleading of 14 April 2023:

  That the ruling confirms the legal position on which Teva is basing its arguments, as expressed in, *inter alia*, in T 488/16 BMS/dasatinib.

That post-published evidence may not be disregarded for purposes of substantiating a technical effect *solely* on the ground that such evidence had not been public before the filing of the relevant patent application. Hence, the decisive question is when a patent applicant or proprietor may rely on such evidence to substantiate a technical effect. According to the EBoA, it is permissible to rely upon a technical effect if the skilled person, having common general knowledge in mind, and based on the application as originally filed, would have considered such technical effect to be encompassed by the technical teaching and embodied by the same originally disclosed invention as is described in the application as filed

Teva is of the view that this clearly does not apply in the present case.

BMS's statement of claim

1. The Court to find in favour of Bristol-Myers Squibb Holdings Ireland Unlimited Company.

2. Teva Pharmaceutical Industries Ltd. and Teva Norway AS to be ordered to pay the legal costs of Bristol-Myers Squibb Holdings Ireland Unlimited Company.

The assessment of the Court

Introduction
The case concerns the validity of granted Norwegian patent NO 558 and supplementary protection certificate SPC/NO 021. The patent protects the product apixaban and pharmaceutically acceptable salts thereof. Apixaban is the active substance in BMS's medicinal product Eliquis, which is an anticoagulant.

Section 52, Sub-section 1, No. 1, of the Patents Act provides that a patent may be invalidated by judgment if,*inter alia,* it has been granted despite the requirements laid down in Sections 1 and 2 not having been met.

According to Section 2, Sub-section 1, of the Patents Act, a patent may only be granted for "inventions which are new in relation to what was known before the filing date of the patent application and which also differ essentially therefrom".

It is not disputed that the novelty requirement in Section 2 of the Patents Act is met. Teva's arguments relate, on the other hand, to the inventive step requirement - i.e. whether the invention differs essentially from what was already known. As an alternative approach, Teva has referred to the requirement in Section 1 of the Patents Act that the invention must be susceptible of "industrial appcliation".

The industrial application requirement is held to implicitly include a requirement that the invention must exhibit a technical effect - in other words, that the invention must work. The technical effect requirement is also partly related to Section 8, Sub-section 2, third sentence, of the Patents Act, which stipulates that the description shall be sufficiently clear to enable the skilled person to carry out the invention on the basis thereof. The requirement is also related to the inventive step assessment. The inventive step must relate to the part of the patent that solves the problem and to whether the patent works, i.e. exhibits a technical effect.

The assessment called for in relation to these requirements is concurrent in scope and has in practice been formulated as a plausibility requirement. Following the ruling of the Enlarged Board of Appeal ("EBoA"), "plausibility" is not considered an independent patentability requirement. The Court will

revert to that ruling later on in this judgment. The cut-off date for the inventive step assessment is the filing date (priority date) of the patent application, which is 21 September 2001.

The Court has full jurisdiction over the issue of whether the inventive step requirement is met, provided, however, that its ruling shall be based on a discretionary technical assessment. The Supreme Court has observed that the courts should exercise restraint in their judicial review of the discretionary technical assessments of the Norwegian Industrial Property Office, cf. Rt-1975-603 (Swingball judgment) and Rt-2008- 1555 (Biomar judgment). The principle of restraint is of particular importance in cases where the basis for the ruling is predominantly the same as it was before the patent authorities, cf. LB-2018-72158-2. In the present case, the factual basis presented before the District Court is broader than that available during the proceedings before the Norwegian Industrial Property Office and the EPO.

Validity of NO 558

Details on the legal premises

Section 2, Sub-section 1, of the Patents Act stipulates that it is a requirement for patentability that inventions "differ essentially" from what was known before the filing date of the patent application. This requirement must be understood in the sense of "not obvious to the skilled person", see Stenvik, *Patentrett* ["Patent Law"], 4th edition, 2020, page 215. There must be a certain leap in technical development, see Stenvik, Gyldendal Rettsdata - The Patents Act, Note 36 on Section 2 (note last revised on 18 November 2019).

This implies that the invention must not have been obvious to the skilled person, based on the state of the art as at the application date. This must be based on an objective assessment without any element of hindsight. The inventive step assessment shall take into account the state of the art as a whole, and not only the closest prior art. If the inventive step requirement is not met, the patent shall be invalidated pursuant to Section 52, Sub-section 1, No. 1, of the Patents Act.

The so-called "problem-solution approach" is used in assessing whether the inventive step requirement is met, cf. Part C, Chapter IV, Section 5.5, of the Patent Guidelines, which corresponds to the EPO Guidelines on the "problem-solution approach" (PSA), cf. the EPO Guidelines.

The first stage of this process is to determine the closest prior art (stage 1). In practice, this will be the publication that would have constituted the most promising starting point for a development leading to the invention. Next, the problem objectively solved by the invention needs to be formulated. This involves studying the difference between the technical results achieved by the invention and those achieved by practising the solution in the closest prior art. In order to obtain a patent, a new or improved effect must be demonstrated (stage 2). And finally, it needs to be considered whether it was obvious to the skilled person, starting from the closest prior art, to solve the problem by the means defined in the patent claim (stage 3).

It is stage 2 - the formulation of the objective technical problem- that is the main focus of this case. A patent application needs to disclose a relevant application and substantiate that the effect is actually achieved - the technical effect requirement.

In this context, there is disagreement between the parties with regard to the requirements applicable to contents of patent applications in the pharmaceuticals field and with regard to when the patent applicant may substantiate technical effect through post-published evidence.

On the scope for relying on post-published data

In Stenvik, *Patentrett* ["Patent Law"], 4th edition, 2020, page 144, the following is stated on this topic:

"If it is necessary for the assessment of an invention for which a patent application has been filed, the Norwegian Industrial Property Office may order the applicant to submit a model, sample, or the like, or to arrange for examinations or tests to be carried out, cf. Section 32 of the Patent Regulations.
Supplementary documentation on the technical effect of the invention may be submitted at a later date, e.g. documentation on efficacy, benefits, etc. However, the invention cannot be exclusively substantiated by such materials. 303 [note: T-1329/04 John Hopkins]. A vague indication which is subsequently substantiated by experimental data will not suffice. 304 [note: T -609/12 Salk Institute]. The technical effect of the invention must already at the time of filing the application be shown to be probable to such an extent that it appears plausible to the skilled person that the effect would be achieved. 305 [note: NU 1963: 6, p. 199]. The effect must not necessarily be documented as at the application date, but it needs to be plausibly substantiated. 306 [note: Human Genome Sciences v. Eli Lilly [2011] UKSC 51]. The invention needs to be practicable and it must on the application date appear plausible to the skilled person that the claimed effect is achieved by working the invention:

"It is sufficient if an 'educated guess' suggests that the effect is achieved, or that the effect is 'reasonably credible', ... Hence, it is not necessary for the application to include experimental data, unless doubts may be raised with regard to the technical effect of the invention, ... In the same way as for the description requirement, ... the application may be supplemented by common general knowledge in the art as at the application date." 307 [LB- 2014-117680]".

Furthermore, the following observations are made in the legislative history of the Patents Act; Legislative Proposition No. 36 (1965 - 1966), pages 19-20:

"A question of particular importance for medicinal products is what documentation of the technical effect should be required for patentability. It is unlikely that any general rule on this can be formulated, as also noted by the committees. Hence, as far as medicinal products are concerned, one should often be able to accept the applicant's own statement on the therapeutic effect as sufficient."
Consequently, the general rule under Norwegian law is that the requirements with regard to documentation of effect are not particularly strict. It is not necessary for the application to include experimental data, unless doubts may be raised with regard to the technical effect of the invention.

In connection with an appeal case pending before the EPO; T 0116/18 (Syngenta), questions have been referred to the EPO Enlarged Board of Appeal ("EBoA") regarding the scope for relying on post-published evidence in the assessment of a patent's technical effect and inventive step. This was done under reference to variations in EPO case law with regard to the issue of whether post-published data may be relied on to substantiate technical effect.

The Technical Board of Appeal had defined three potential plausibility standards:

- no plausibility: No restriction on the scope for relying on post-published evidence of technical effect**.**
- ab initio implausibility: Post-published evidence may be relied on, unless the skilled person would have had a "significant reason" to doubt the technical effect.
- ab initio plausibility: Post-published evidence may be relied on if the skilled person would have considered the technical effect to be plausible.

The ruling of the Enlarged Board of Appeal was handed down on 23 March 2023. The EBoA order is worded as follows:

"1. Evidence submitted by a patent applicant or proprietor to prove a technical effect relied upon for acknowledgement of inventive step of the claimed subject-matter may not be disregarded solely on the ground that such evidence, on which the effect rests, had not been public before the filing date of the patent in suit and was filed after that date.

2. A patent applicant or proprietor may rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention."

In its ruling, the EBoA affirms the principle of free adduction of evidence, and that the technical effect assessment will depend on the facts of each case. Consequently, evidence submitted by a patent applicant or proprietor to prove the technical effect relied upon for acknowledgment of inventive step may not be disregarded *solely* on the ground that such evidence had not been public before the filing date of the patent and was filed after that date

The referring ruling included a detailed discussion of the terms "ab initio plausibility" and "ab initio implausibility". The EBoA, on the other hand, abandons "plausibility" as a concept. The EBoA held that the term "plausibility" does not amount to a distinctive legal concept or a specific patent law requirement under the European Patent Convention ("EPC"). Hence, the decisive factor is an assessment of what the skilled person, on the basis of the patent application as at the filing date, and having common general knowledge in mind, would understand from the application as the technical teaching of the claimed invention.

A question that may be raised in the wake of the EBoA ruling is what it means that an effect is "based on the application as originally filed" and "embodied by the same originally disclosed invention", cf. the EBoA order. The EBoA provides no further guidance on this and acknowledges the abstractness of the criteria.

As far as the present case is concerned, the Court is of the view that the claimed technical effect was encompassed by the technical teaching and embodied by the originally disclosed patent application. The Court considers apixaban to be a plausible invention. Nor did the skilled person have any reason to doubt the effect, even without biological data. The invention being considered plausible does in any event satisfy the new criteria formulated by the EBoA for the inventive step assessment. Post-published evidence may thus be taken into account for purposes of substantiating inventive step. The Court therefore sees no need for elaborating on what may be inferred from the EBoA ruling.

Similarly, the Court therefore considers that the Court of Appeal ruling, in the appeal proceedings in the parallel invalidity action in the United Kingdom, also has no bearing on the Court's conclusion in the present case.

Patent NO 558 and patent application WO 652 The patent is entitled:

"*Lactam-containing compounds, pharmaceutical compositions containing the same, such compounds for use in therapy, as well as the use thereof in the manufacture of medicaments for the treatment of*

disorders".

Claim 1 (FB page 486) is worded as follows:

"*Compound, characterised in that it is represented by formula (I):*

[Diagram not included in judgment]

or a pharmaceutically acceptable salt thereof."

The field of the invention is described as follows in the introductory part of the patent:

"*The present invention relates generally to lactam-containing compounds and derivatives thereof which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical preparations containing the same, and methods of using the same as anticoagulant agents for treatment of thromboembolic disorders*" (page 1, lines 1-6, FB page 250).

The role of factor Xa in the coagulation cascade is explained as follows on pages 5-6, line 20 (FB page 254) *et seq.*:

"*Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by the formation of prothrombinase complex (factor Xa, factor V, CA*$^{2+}$*> and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin* [(...)], *inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system*".

Hence, this suggests that factor Xa may be an appropriate target for an anticoagulant, inasmuch as inhibition of factor Xa leads to interruption of the blood coagulation cascade by suspending the generation of thrombin from prothrombin.

The patent goes on to explain that: "*[t]herefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors. In addition, it is also desirable to find new compounds with improved pharmacological characteristics compared with known factor Xa inhibitors*" (page 6, lines 4-8, FB page 255).

Reference is thereafter made to a number of advantageous drug-like properties, including, *inter alia*, low dosage, factors which reduce blood concentration peak-to-through characteristics, lower clearance, increased concentration of active drug at the receptor (reduced volume of distribution) and decreased potential for adverse side effects. On page 6, lines 28-30, it is disclosed that new lactam-substituted compounds with such properties have been discovered.

The following is stated in the summary of the invention (page 7, lines 13 -27, FB page 256):

The present invention provides a novel method comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder.

"The present invention provides novel lactam-containing compounds and derivatives thereof for use in therapy.

The present invention provides the use of novel lactam-containing compounds for the manufacture of a medicament for the treatment of a thromboembolic disorder.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that lactam-containing compounds of Formula I:
P4 - P - M - M4
I
wherein P4, P, M and M4 are defined below, or pharmaceutically acceptable salt or prodrug forms thereof, are effective factor Xa inhibitors."

This is followed by a detailed description of preferred embodiments. The claims in NO 558 only specify apixaban, but the description also lists a number of other lactam-substituted compounds that were investigated in the research phase. Embodiment 8 consists of a group of 74 compounds (pages 63-70), including apixaban, which is specified below, and takes the following form (page 64, lines 17-18, FB page 313).

"*1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl)phenyl]-4,5,6, 7-tetrahydro-1 H-pyrazolo[3,4-c] pyridine-3-carbonitrile*"

On page 111, lines 17-19 (FB page 360), the following is stated on the utility of the invention:

"*The compounds of this invention are inhibitors of factor Xa and are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals (i.e., factor Xa-associated disorders).*"

Thereafter, on page 112, it is described that the effect of the compounds of the invention has been tested in vitro. Moreover, it is stated on page 113, lines 13-21, that a number of compounds were tested and that these were effective as Xa inhibitors.

"Compounds tested in the above assay are considered to be active if they exhibit a Ki of < 10μM. Preferred compounds of the present invention have Ki of < 1 μM. More preferred compounds of the present invention have Ki of < 0.1μM. Even more preferred compounds of the present invention have Ki of < 0.01μM. Still more preferred compounds of the present invention have Ki of < 0.001 μM. Using the methodology described above, a number of compounds of the present invention were found to exhibit Ki of <10μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors."

Pages 128 to 237 (FB page 377 et seq.) provide a detailed explanation of the synthesising process (production of the chemical compounds) for 110 compounds, with the patent including a total of 140 embodiments.

The synthesis and characterisation of apixaban is described in Example 18 on pages 154 to 156 (FB page 403). It is disclosed on page 156, line 10, that 3.07 grams of apixaban were produced.

The assessment as to whether the invention in NO 558 has inventive step shall be made on the basis of the patent application on which the invention was based, i.e. WO 652. The question is what can be derived therefrom, having common general knowledge in mind.

Patent application WO 652 (FB page 1609) is entitled "Lactam-containing compounds and derivatives thereof as factor Xa inhibitors". During the proceedings, the parties have partly referred to the Norwegian application instead, i.e. NO 163 (FB page 636).

The application is a 439-page document, which includes a Markush formula (generic formula) in Patent Claim 1 that encompasses a very large number of potential chemical compounds, subsequent to which that claim was limited to a single compound - apixaban - during the application process.

Apixaban appears in Embodiment 8 (out of a total of 15), and consists of a group of 74 compounds (FB page 1677 et seq.)

Besides, the application makes reference, under "Background of the Invention" on page 2 (FB page 1611), to previous literature and patent applications, including WO 00/39131 ("WO 131"), which the parties agree is the closest prior art, and to which the Court will revert in more detail below.

- The skilled person

The identity of the skilled person is of significance in several patent law contexts, including in the inventive step assessment. Determining the identity of the skilled person is also of significance for determining what is considered common general knowledge in the art.

In making the said assessment, the person of average skill in the art is used as a benchmark. The skilled person has complete overview of the state of the art as at the application date and has the ability to utilise the known materials in a sound professional manner, but is without innovative abilities, cf. Stenvik, Patentrett ["Patent Law"], 4th edition, 2020, pages 198-199.

According to Part C, Chapter IV, Section 5.3, of the Patent Guidelines, the skilled person is "presumed to be a practising practitioner in the relevant field of technology, who is possessed of average knowledge and ability and who is aware of what was common general knowledge in the art at the relevant date". The skilled person cannot be assumed to have unlimited ability to make combinations, i.e. the ability to combine known elements into new solutions, and thus does not possess inventive ability, cf. LB -2015-90322. For complex inventions, the skilled person may also be considered as a group of persons, cf. LB-2008-066692.

The parties essentially agree on the skilled person in the present case. The Court will proceed on the basis that the skilled person is a team with knowledge of factor Xa inhibitors and expertise in medicinal chemistry biology/biochemistry, pharmacology, pharmacokinetics, safety and clinical medicine.

- Common general knowledge in the art

Common general knowledge in the art relates to the level of knowledge that the defined skilled person is assumed to possess based on his/her education and general knowledge accumulated throughout his/her professional life. It typically includes the contents of standard textbooks and reference books, but the contents of databases that are readily accessible and commonly used also form part of common general knowledge in the art. Protected trade secrets, specialised knowledge, certain articles or conference presentations, specific patent documents or scientific articles fall outside the scope of common general knowledge in the art.

In connection with a parallel case, before the High Court of England and Wales, Patents Court, between Teva (and Sandoz Ltd.) on the one hand, and BMS on the other hand, the parties submitted an agreed document on common general knowledge in the art as at the application date. Teva and BMS agree that this document is to be used as an agreed document in the present case as well (FB page 3048 and FB 3094 in Norwegian version).

Common general knowledge in the art included, *inter alia*, SAR work and knowledge of techniques and methods for structure-based design, based on 3D structures of active sites of enzymes, irrespective of whether these were generated via X-ray crystallography or computer modelling.

In this case, the parties agree on what constitutes common general knowledge in the art. However, their disagreement relates to how the skilled team would have read/understood the patent application based on common general knowledge in the art.

- What was known from common general knowledge in the art/the prior art

In 2001, a number of pharmaceutical companies reported having developed factor Xa inhibitors.

Factor Xa is an enzyme that converts prothrombin to thrombin. Thrombin cleaves fibrinogen into fibrin, which together with platelets forms blood clots

The challenge was to identify a compound that was potent, selective and had the properties required for an oral drug.

A number of compounds were found to be potent factor Xa inhibitors with Ki or IC50 values in the nanomolar (and even below 1 nM) range. Ki and IC50 are measures of enzyme inhibitor potency - the lower the value, the more potent. The more potent the inhibitor, the better it is able to inhibit the activity of the enzyme - and the less of the compound is needed.

Their selectivity with respect to thrombin and trypsin was often reported to be high, and in vivo data from animal models were described for some compounds. Selectivity is, as described earlier in this judgment, how well a medicinal product acts on different receptors.

An orally bioavailable factor Xa inhibitor would be preferable to one that had to be administered parenterally (outside of the digestive tract). An oral drug needs to have drug-like properties. This means, for example, good solubility, good permeability (permeability of the cell membrane to various substances) and activity after oral administration, and a half-life that makes the drug suitable for once- or twice-daily dosing.

Published X-ray structures of factor Xa inhibitors were available that could be used for structure-based design of effective inhibitors. This applies to the design of both the three-dimensional structure of the molecules and their key interactions with the S1 and S4 binding pockets.

The method for improving the properties of a molecule by generating structure-activity relationship (SAR) work was part of common general knowledge in the art. Based on this knowledge, better and better factor Xa inhibitors could be produced. SAR data can be based either on published data, or on own generated data, or a combination of both.

- Known factor Xa inhibitors on the priority date

On the priority date, a number of factor Xa inhibitors were known, cf. FB page 2040 *et seq*., which includes a number of scientific publications. Some key compounds are represented by DX-9065a; Figure 5 below.
DX-9065a is discussed in more detail in an article entitled “Factor Xa inhibitors- a review of the recent patent literature”, Uwe J Ries & Henning WM Priepke” (FB page 2309 *et seq.*). The article gives an overview of patent literature and research reports relating to factor Xa inhibitors, which were published over the period from January 1999 to June 2000. DX -9065a was an early potent factor Xa inhibitor, but did not have the desired drug-like properties, primarily due to poor bioavailability. The reason for this was that the molecule is charged at physiological pH. The charge comes from the strongly basic amidine groups.

[Diagram not included in judgment]

A next step in the development can be represented by DPC 423. Figure 6, which is discussed in the same article (FB page 2309 et se.) . DPC 423 is therein described as one of the most important advances in the search for oral factor Xa inhibitors at the time of its discovery. In DPC 423, the strongly basic amidine groups have been replaced at a weakly basic benzylamine substituent in P1, resulting in improved drug- like properties.

[Diagram not included in judgment]

W) 131 builds on compound DPC 423, WO 131 pertains to factor XA inhibitors with a bicyclic nitrogen containing core composed of a 5-ring and a 5-7 ring. WO 131 has 109 exemplified compounds, in 35 of which compounds the core looks as in Figure 7.

[Diagram not included in judgment]

Regarding WO 131, the following is stated on page 2 of the patent application (FB pages 638 and 639, Norwegian version) :

> "WO00/39131 describes heterobicyclic factor Xa inhibitors of which the following is an example formula: […the chemical formula is inserted…], wherein Z is C or N, G is a mono- or bicyclic group, A is a cyclic group and B is a basic group or a cyclic group. Compounds specifically described in WO00/39131 are not considered to be part of the present invention."

A comparison of DPC 423 with WO 131 shows that a step- by- step optimization has taken place. Consequently, a further subsequent step in the development is represented by patent application WO 131, which the parties also agree is the closed prior art to NO 558. Example 61 from WO 131 (Figure 8) represents an example structure of the closest prior art to NO 558. Example 61 from WO 131 (Figure 8) represents an example structure of the closest prior art, cf Figure 6. The skilled person will recognise that the structure of DPC 423 is rigidifed through a cyclisation in the centre of the molecule, while a weakly basic benzyl group in P1 is retained.

[Diagram not included in judgment]

Hence, both DPC 423 and WO 131 are precursors to the development of apixaban.

Embodiment 8 of the patent appcliation is itself built on WO 131. Many of the examples in WO 652 are based on cores in WO 131.

Specific assessment – Inventive step/industrial application
The Court is adopting the "problem- solution approach" for its inventive step assessment.

1. The closed prior art
The parties agree that the closes prior art, which would have constituted the most promising starting point for a development leading to the invention, is WO 131 (FB 1276).

WO 131 is the publication of international patent application PCT/US 99/30316, filed on 17 December 1999 by Du Pont Pharmaceuticals Company, the legal predecessor of BMS. Hence, WO 131 originates from the same research group as WO 652.

WO 131 is entitled “Nitrogen Containing Heterobicycles as Factor Xa Inhibitors”. The application pertains to factor Xa inhibitors with a bicyclic nitrogen-containing core consisting of a 5-ring and a 5-7 ring.

WO 131 describes a large number of compounds in the form of a Markush formula. The patent application includes 109 exemplified compounds (pages 96 to 206).

Some of the compounds have a core structure similar to that of apixaban, but none of the examples have a lactam substituent at the P4 position, as does apixaban.

The Court will proceed on the basis that WO 131 is the closest prior art.

II. The objective technical problem

Based on WO 131, as the closest prior art, the Court will first establish the technical problem to be solved by the skilled person. Part C, Chapter IV, Section 5.5.2, of the Patent Guidelines describes the technical problem as “the aim and task of modifying or adapting the closest prior art to provide the technical effects that the invention provides over the closest prior art”.

As mentioned above, the patent application needs to document that an invention has been made that is susceptible of industrial application, cf. Section 1, Sub-section 1, of the Patents Act. This implies a requirement that the invention shall have technical effect, i.e. that it provides a solution to the technical problem it aims to solve.

It is not disputed that the patent application provides sufficient information to manufacture and test apixaban. It is also not disputed that efficacy and pharmacokinetic properties are documented by post-published evidence.

Based on the description in the patent application, the Court will proceed on the basis that a technical problem the invention aimed to solve was to provide an effective factor Xa inhibitor with improved properties for the treatment of thromboembolic disorders (WO 652, pages 6 and 7, FB 1615 and 1617).

- The issue of whether the patent application has made a contribution to the state of the art

Teva has argued that it does not appear plausible that a contribution to the state of the art has been provided through the patent application. Teva’s line of argument is as follows: The application disclosed a general Markush formula comprising a very large number of potential chemical compounds, only a few of which had been synthesised, and 140 specific compounds are included in the example section. Without biological data that substantiate efficacy, it is not plausible to the skilled person, as at the application date, that the compounds, including apixaban, are potentially useful factor Xa inhibitors.
The Court does not agree with this. The Court will set out its reasons below.

The assessment is based on the contents of patent application WO 652, as understood having common general knowledge in mind, as at the priority date of the patent; 21 September 2001.

In the understanding of the Court, the issue before it is that of whether apixaban solves the problem at which the invention is aimed. The Court is of the view that this is not a matter of plausibility for all compounds in the application, as claimed by Teva. The Court refers to T 488/ 17 (Dasatinib), paragraph 4.2 (FB page 1156), where it is stated that the assessment pertains to the “claimed subject-matter”. The disputed application in Dasatinib concerned a large number of compounds encompassed by a Markush formula (like the application in the present case) with 580 compounds, including Dasatinib. The following is quoted from that ruling (emphasis added by the Court):

> "It is established jurisprudence of the boards of appeal that the assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common general knowledge then available to the skilled person. Post-published evidence in support that **the claimed subject-matter** solves the technical problem the patent in suit purports to solve may be taken into consideration, if it is already plausible from the disclosure of the patent that the problem is indeed solved (see Case Law of the Boards of Appeal, 8th edition, I.D.4.6; T 1329/04, point 12 of the Reasons; T 1043/1 0, point 12 or the Reasons).
>
> Thus, for post-published evidence to be taken into account, it is necessary to establish whether or not the asserted activity has been made sufficiently **plausible for dasatinib** at the effective date of the patent in suit. Basis for this assessment is the application as filed and the common general knowledge of the person skilled in the art at the filing date."

Consequently, the Court's assessment as to whether the inventive step requirement is met only encompasses apixaban, and not all the other compounds in the patent application.

In making its assessment, the Court has found the testimony of BMS's expert witnesses (Professor Klaveness and Dr Young) to be of most relevance to this case. Dr Young showed how medicinal product development is conducted in practice, in particular the development of protease inhibitors and inhibitors targeting factor Xa. In his testimony, he provided detailed information on the tools and strategies used in the development of factor Xa inhibitors leading up to the development of apixaban. He also rendered testimony on the considerations made in the selection and optimisation of the lead substances, and why. Professor Klaveness rendered testimony on the basis that existed for specifying the properties that factor Xa inhibitors needed to make a contribution to the state of the art. As far as Teva's expert witnesses are concerned, it is noted that Professor Meijers, Dr Judkins and Professor Grøtli did not have the same experience with the development of a factor Xa drug and/or other protease inhibitors. Professor Meijer's expertise is in the field of coagulation, which is of relevance to the biological effects of factor Xa inhibitors, while
Dr Judkins and Professor Grøtli are both medicinal chemists, but had not worked directly with the development of protease inhibitors and the medicinal product development strategies used industrially.

Much of the court hearing was centred on assessments of the significance of the IC50 value, selectivity and other parameters in the development of apixaban. BMS's witnesses also clarified the significance of other information, such as the quantity of substance synthesised and the effort required to obtain a larger amount of a pure substance. The Court notes that this is important for conducting in vivo studies.

Based on the evidence presented, the Court is of the view that the skilled person/skilled team would have made the following assessment of the patent application, having common general knowledge in mind:

The skilled person reading WO 652 would first note that the patent application relates to factor Xa inhibitors and that the aim is to identify effective and specific factor Xa inhibitors, with improved pharmacokinetic properties.

Furthermore, the skilled person would note the detailed descriptions of the synthesis and characterisation of the 110 compounds that had been produced in the laboratory, and that these included the 74 compounds of Embodiment 8. In order to shed further light on the 74 compounds included in Embodiment 8, the Court has inserted a structural analysis below. All compounds have the same core and a lactam in the P4 group. The figure (Figure 9) illustrates the common core and different variations in the P1 and P4 groups

[Diagram not included in judgment]

The skilled person would have understood that the 74 similar compounds in Embodiment 8 and Patent Claim 8 were the results of a lengthy optimisation effort, from DPC 423 and continued in WO 131, with the most promising groups from WO 131 having been included in the next stage of the optimisation effort. From the structures of the substances, it would be clear to the skilled person that WO 652 represented a continuation of previous efforts.

The skilled person would note that apixaban shares important structural elements with certain other known factor Xa inhibitors. The skilled person would also assess the drug-like properties of apixaban on the basis of its chemical structure.

Apixaban has a P4-core-P1 structure. The skilled person would be aware that potent factor Xa inhibitors had an L-shaped conformation linked by a central core. The skilled person would know that this was considered necessary in order to place the P1 and P4 groups in their respective binding pockets, i.e. S1 and S4.

Apixaban has neutral P1 and P4 groups and the skilled person would know that factor Xa inhibitors that are neutral are of particular interest for achieving oral bioavailability. Apixaban has a methoxyphenyl group at the P1 position and a lactam substituent at the P4 position. As noted in the title of the patent application;
"lactam-containing compounds [...] as factor Xa inhibitors", this substituent is specific to the invention.

The skilled person would recognise the similarity between apixaban and the DPC 423 structure (Figure 6 above). Apixaban's core is a rigidified version (stronger bond) of the core of DPC 423. In addition, the weak benzylamine group of P1 has been replaced by the neutral methoxyphenyl group, and the methylsulfonylphenyl group of P4 has been replaced by a lactam group. Hence, the P1 group in apixaban is in line with the general development from strongly basic P1 in DX -9065a; Figure 5, towards a weakly basic P1 group as previously used in, *inter alia*, DPC 423. Furthermore, the P4 group in apixaban was a plausible isostere (molecular or atomic groups with similar size and electron distribution) for the P4 group in DCP 423. Based on the knowledge of the S4 binding pocket, the skilled person would know that there was a possibility of modifying the methylsulfonylphenyl group at the P4 position in DPC 423. These modifications would be of particular interest for an effective neutral factor Xa inhibitor with improved drug-like properties.

Moreover, the skilled person would note that apixaban differs from WO 131, in that the P4 group is modified and in that the trifluoromethyl group in the central bicyclic ring has been changed to an acetamide group, which results in more favourable drug-like properties, such as lower molecular weight and lesser lipophilicity.

The structure of apixaban is consistent with the skilled person□s knowledge of the SAR for potent factor Xa inhibitors as at the application date

Furthermore, reference is made to the patent application, page 170, lines 21 to 22 (FB page 1779), where the following is stated: "Compounds tested in the above assay are considered to be active if they exhibit a Ki of ≤ 10 μM." Moreover, more preferred values of Ki are listed before it is stated in line 26 that: "Still more preferred compounds of the present invention have Ki's of ≤ 0.001 μM". It is thus expressly stated in the application that the most preferred compounds are potent factor Xa inhibitors.

The skilled person would understand that the compounds produced had been tested in the usual manner, and that several of the compounds had turned out to be effective factor Xa inhibitors. Furthermore, the skilled person

would understand that the compound of Example 18; apixaban, had been selected for further studies because it had shown promising results in initial tests, as an effective factor Xa inhibitor.

The skilled person would have noted that apixaban is the only compound that had been produced in a large

quantity. In all the examples in WO 652, quantities produced range from 1 to 424 mg, with the exception of Example 18, which is apixaban, where 3,070 mg (3.07 grams) is produced. The skilled person would have noted the large quantity of 3.07 grams. Apixaban was not only produced in a large quantity, but had been subjected to further purification and recrystallisation steps. These steps are necessary to produce a pure material for further pharmacokinetic studies and preclinical development studies of potential medicinal products.

The Court notes that the synthesis process in Example 18 consists of six synthesis steps, with a low total yield of 1.3%. This is a demanding process, in which intermediates were produced in several rounds. It is often more demanding to produce larger quantities of chemical substances than smaller ones. The skilled person would understand that the production must have been based on a deliberate process and that Example 18 (apixaban) was the most promising substance, and that in vivo animal studies with this substance had probably been planned or performed. Consequently, it is plausible to the skilled person that apixaban had sufficiently good selectivity for the antithrombotic effects to be studied in vivo.

The Court is of the view, based on the above, that the skilled person would have considered apixaban to be a plausibly effective factor Xa inhibitor.

It is therefore permissible to rely on post-published evidence. There is agreement that post-published evidence confirms the effect.

The conclusion of the Court is that the problem as formulated in the patent has thereby been solved

The objective technical problem can thereby be formulated as follows: to provide an effective factor Xa inhibitor for the treatment of thromboembolic disorders, with improved properties.

- The issue of whether apixaban provided a technical contribution over WO 131

As an alternative basis for lack of inventive step, Teva has argued that NO 558 does not provide a technical contribution over WO 131, even if the invention was plausible.

WO 131 describes a large number of compounds in the form of a Markush formula, which are stated to be useful as factor Xa inhibitors. There is agreement that some of the compounds have a core structure similar to that of apixaban, although apixaban is not specifically indicated.

Teva has argued that there is nothing in the WO 652 application to suggest that improved factor Xa inhibitors have been provided, compared to the compounds encompassed by WO 131. It is argued that WO 131 and WO 652 describe the compounds as being entirely equivalent in terms of activity against factor Xa and other inhibition of serine proteases. Teva has argued that apixaban is thus an arbitrary selection from the compounds encompassed by WO 131, and that it constitutes an unlawful so-called selection invention.

Selection inventions are inventions where the more recent patent is a particular variant of a previously known, but more generally specified, technical solution. Or it may represent a particular choice from a number of potential combinations specified in an earlier citation. This is especially relevant for chemical compounds, which are often specified in the form of general formulae or designations.

Selection inventions are addressed in Part C, Chapter IV, Section 5.12, of the Patent Guidelines, which stipulates that the inventive step requirement is met in the following circumstances:

> "The subject-matter of the application in selection inventions differs from the closest prior art in that it represents selected individual elements, subsets or sub-ranges. If this selection is related to a particular

technical effect, and if there is nothing to point the skilled person to making that selection, the inventive step requirement will be met. This technical effect that occurs within the selected scope may also be the same effect that is achieved within the broader known scope, but to an unexpected degree."

Teva has argued that apixaban must exhibit advantageous properties over the compounds generally encompassed by the Markush formula in WO 131. The Court is of the view that the comparison of the properties must be made on the basis of the structurally most similar compounds, and not the broader group of compounds encompassed by the Markush formula. The Court refers, in this regard, to T 181/82 (Spiro compounds), where it is stated that comparative tests must be compared to the structurally most similar compounds. Corresponding observations are made in T 187/86, where the following is stated:

"The principles laid down in the highly relevant " Spiro compounds" decision (T 181/82, OJ EPO, 1984, 401) require that where comparative tests are submitted as evidence of an unexpected effect, there must be the closest possible structural approximation in a comparable type of use to the subject-matter claimed."

Reference is also made to a letter of 9 September 2008 from BMS□s patent attorneys, Carpmaels & Ransford, to the EPO. It is evident from the letter that BMS submitted comparative data during the processing of the application by the EPO, showing that the factor Xa inhibitory activity (Ki) of apixaban is better than the inhibitory activity of the examples provided in WO 131. The following is quoted from the said letter (FB page 1191):

"[...] the Applicant submits herewith comparative data demonstrating the unexpectedly superior activity of the presently claimed compound relative to the closest compounds disclosed in D3.

[...]

"Of the compounds disclosed in D3 [WO 131; comment added by the Court], Examples 6, 10, 13 and 99 share three elements that are common to the presently claimed compound, whereas all other examples disclosed in D3 contain two or less elements that are common to the presently claimed compound.
Accordingly, Examples 6, 10, 13 and 99 of D3 (hereinafter □the D3 Examples□) represent the structurally closest compounds to the present invention. The data submitted herewith establish that the Factor Xa inhibitory activity (Ki) of the presently claimed compound is superior to the inhibitory activity of the D3

The data submitted herewith establish that the Factor Xa inhibitory activity (Ki) of the presently claimed compound is superior to the inhibitory activity of the D3 Examples. The Factor Xa activity was determined using the assay set out on page 169, line 22 to page 170, line 32 of the present application.
The data establish that the inhibitory activity of the presently claimed compound (Example 18) is unexpectedly significantly better (by at least an order of magnitude) than the D3 Examples. It is therefore submitted that the data fully support recognition of an inventive step in respect of the claimed compound".

The Court is of the view that a low Ki value was also not decisive in itself, as the decisive concern was to find compounds with the right balance between the necessary properties. The skilled person would therefore also have attached importance to properties other than potency, such as lower molecular weight, lower pK_a (neutral molecule with pH 7.4), pharmacokinetic properties: absorption, distribution, metabolism, excretion ("ADME"), low protein binding, lipophilicity, solubility, high concentration of inhibitors at the receptor, and a plasma concentration profile which showed that apixaban has improved drug-like properties compared to neighbouring compounds in WO 131. On this basis, the skilled person would have understood that apixaban has improved properties compared to WO 131.

Conclusion

NO 558 provided a technical contribution over WO 131.

III. The issue of whether the solution was obvious

The third stage of the problem-solution approach is then whether it was obvious to the skilled person, starting from the closest prior art, WO 131, to solve the problem by the means defined in the patent claim.

It is undisputed that the solution was not obvious if the problem is formulated as stated above. Hence, there is agreement that there was nothing in WO 131 that led the skilled person to apixaban, and the inventive step requirement is thus met.

The Court nevertheless refers to the expert report by Dr Young (FB 2791, paragraphs 7.10 to 7.11), and his observations therein on the obviousness assessment, which are endorsed. The observations are worded as follows:

> "WO 131 contains no guidance that would have led the skilled person towards this approach suggested by Dr Judkins, let alone towards the specific P4 substituent of apixaban. To arrive at apixaban based on WO 131, the skilled person would need to make the following choices:
>
> i. A pyrazolopiperidone core structure has to be chosen;
> ii. A methoxyphenyl must be chosen for the P1 position;
> iii. A carboxamide must be chosen as the substituent on the core;
> iv. A particular lactam needs to be chosen for the P4 position.
>
> There is no information in WO 131 that would prompt the skilled person to make these choices, nor any information that would otherwise guide the skilled person towards an alicyclic compound such as piperidinone, or pyridone based on the nature of the exemplified P4 substituents in WO 131.

Conclusion on the issue of inventive step

On this basis, NO 558 cannot be invalidated pursuant to Section 52, Sub-section 1, No. 1, of the Patents Act.

The issue of whether the application has been unlawfully amended

Teva has argued that the amendment during the processing of the application, to only include apixaban, is an unlawful amendment. This is on the basis that when the protection was limited to apixaban, a selection was made that could not be directly or unambiguously derived from the application.

According to Section 52, Sub-section 1, No. 3, of the Patents Act, a patent may be invalidated if "it contains subject-matter which was not disclosed in the application as filed." This ground of invalidity is closely related to Section 13, which stipulates that: "A patent application shall not be amended in such a way that protection is claimed for subject-matter which was not disclosed in the application at the time it was filed".

The rationale behind this ground of invalidity is two-pronged. One relates to the priority right the applicant obtains when filing a patent application. The other relates to the need for the general public to be able to organise its activities in accordance with existing patents.

The requirement for disclosure in the application documents must be understood to mean that the application after the amendment must fall within the scope of what can be directly and unambiguously derived from the basic documents, supplemented by what is implied by the common general knowledge of the skilled person, as noted in, *inter alia*, Stenvik, *Patentrett* ["Patent Law"], 4th edition, 2020, pp. 80 and 81.

This provision applies to both limitations and extensions of patent protection. Amendments cannot be made if the limitation or selection is held to constitute an "arbitrary selection", cf. Stenvik, *Patentrett* ["Patent Law"], 4th

edition, 2020, p. 81. A selection will not be arbitrary if such selection is expressly mentioned in the basic documents, cf. Part C, Chapter VII, Section 3.4, of the Patent Guidelines.

In the assessment of the Court, the limitation of the patent application, to apixaban, did not constitute an unlawful amendment. Apixaban was "disclosed in the application". The Court notes that apixaban, which is the compound in Claim 1 of the patent, is explicitly described in Example 18 of the application (page 220), and is specified in Claim 8 (page 277 and lines 34-36) of the application. The amendment is within the scope of what the skilled person could infer from the basic documents, having common general knowledge in mind, and the amendment is not considered to be an arbitrary selection. Hence, apixaban could be directly and unambiguously derived from the application. The amendment made to Claim 1 is thus clearly supported by the application as filed.

Consequently, no unlawful amendment has been made that could constitute a ground of invalidity.

Conclusion

There is no basis for invalidating patent NO 558 pursuant to Section 52, Sub-section 1, No 3, of the Patents Act.

Validity of supplementary protection certificate SPC/NO 021

In addition to invalidation of the patent, Teva has also moved for invalidation of supplementary protection certificate SPC/NO 021.

A supplementary protection certificate (SPC) is an extension of the exclusive right that may be conferred on a patent proprietor in respect of medicinal products. Under the SPC Regulation; 469/2009/EU, the protection period for a patented medicinal product may be extended by up to five years. The rationale behind this arrangement is that it can often take a long time to obtain a marketing authorisation for a medicinal product, partly due to the extensive testing that many medicinal products need to undergo before these can be offered for sale or brought to the market. This can result in the proprietor of a medicinal product patent being prevented from marketing the medicinal product for much of the patent protection period. The supplementary protection certificate provisions are intended to compensate for this.

Teva has invoked two sets of grounds in support of its claim for invalidation of the supplementary protection certificate. Both are based on provisions in the SPC Regulation, which has been transposed into Norwegian law, cf. Section 62a of the Patents Act.

The first set of grounds is that basic patent NO 558 is invalid and that the supplementary protection certificate is invalid as a result thereof, cf. Article 15(1)(c) of the SPC Regulation. In this regard, the Court refers to the above discussion, where it was concluded that the basic patent is valid. Hence, Teva cannot prevail with its claim on the said grounds.

The second set of grounds is that Teva considers the supplementary protection certificate to be invalid because it was issued in violation of the provision in Article 3(a), cf. Article 15(1)(a), of the SPC Regulation. Article 3(a) is worded as follows:

> "Article 3. Conditions for obtaining a certificate
> A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:
> (a) the product is protected by a basic patent in force. [...]"

In order for a product to be considered protected by a basic patent, the said product must either be expressly

disclosed in the claims, or the patent claims must pertain to that product, cf. Part C, Chapter V, Section 4.2.2.1, of the Patent Guidelines.

Teva has argued that the product apixaban is not protected by the basic patent, as that product could not be specifically identified on the basis of the patent application.

In support of its view that the supplementary protection certificate should be invalidated, Teva has referred to two rulings (C-121/17 and C-650/17) of the Court of Justice of the European Union ("CJEU").

Case C-121/17 concerned an application for the grant of a supplementary protection certificate for the combination of the active substances tenofovir disoproxil and emtricitabine, where only one of the active substances was identified in the basic patent. The active substance emtricitabine was neither disclosed in the patent claims, nor in the description. The CJEU ruled that the supplementary protection certificate could not be granted as the condition that the product "necessarily fall under the invention covered by that patent" was not met.

Case C-650/17 concerned an application for the grant of a supplementary protection certificate where the relevant active substance had been developed by a licensee subsequent to the granting of the patent application, through an independent inventive activity, which formed the basis for a new patent. Here, the product fell within the scope of a functional definition, but was not individualised as a specific embodiment, which could be derived from the teaching of the patent.

The Court is of the view that the [facts of the] CJEU rulings to which Teva has referred are not comparable to the facts of the present case.

The Court notes that apixaban was, at the application date of SPC/NO 021 (26 September 2011), protected by Patent Claim 1 of basic patent NO 558, which was then in force. Furthermore, it is noted that apixaban is structurally individualised and not only covered by functional specifications. Apixaban was disclosed in Claim 1 of the basic patent (NO 558) and in Claim 8 of patent application WO 652. Apixaban is specifically identifiable, with an exact structure, and is also identifiable on the basis of the information in the patent application.

Consequently, Teva cannot prevail with its claim for invalidation of SPC/NO 021, based on Article 15, cf. Article 3, of the SPC Regulation, either.

Conclusion

SPC/NO 021 cannot be invalidated pursuant to Article 15 of Regulation No 469/2009/EC (the SPC Regulation), cf. Section 62a of the Patents Act.

Declaratory judgment - Apixaban Teva

The Court has concluded above that NO 558 and SPC/NO 021 are valid. It is not disputed that an exploitation of Apixaban Teva would infringe BMS's patent rights if NO '558 and SPC/NO 021 are valid.

Consequently, the Court finds in favour of BMS with regard to Teva's claim for a declaratory judgment to the effect that the exploitation of Apixaban Teva does not constitute grounds for prohibition on the basis of SPC/NO 021 or NO 558

Legal costs

Bristol-Myers Squibb Holdings Ireland Unlimited Company has prevailed in full and is thus entitled to have its legal costs compensated by the claimants, Teva Pharmaceutical Industries Ltd. and Teva Norway AS, cf. Section 20-2, Sub-section 1, of the Civil Procedure Act. There are no weighty reasons that would justify an

exemption from the general rule, cf. Section 20-2, Sub-section 3, of the Civil Procedure Act.

Section 20-5, Sub-section 1, of the Civil Procedure Act stipulates that it is the "necessary costs incurred in relation to the action" that the prevailing party may claim compensation for. In assessing whether the costs have been necessary, weight is attached to whether it has been reasonable to incur these in view of the importance of the case.

On 9 May 2023, Attorney Stenvik submitted a legal cost specification in accordance with applicable statutory requirements, adjusted to include costs incurred in relation to work carried out after the main hearing. Such work was occasioned by the EBoA ruling and the ruling in the parallel invalidity action in the United Kingdom. The said specification puts the total legal cost claim in the case at NOK 9,555,655. This is made up of legal fees in the amount of NOK 6,312,620 and expenses, including expenses in relation to experts, etc., in the amount of NOK 3,243,035.

The amount of the legal cost claim is high, but the amount of the opponent□s legal cost claim is also high. The case has been complex and several experts have been involved in the case on both sides. Nor have there been any objections to the legal fee part of the legal cost specification.

However, Advokat Steinkjer has in a letter of 16 March 2023 objected to BMS's compensation claim in respect of expenses incurred on "legal assistance in the Norwegian action from the law firm of WilmerHale", in the amount of NOK 1,920,404, excl. VAT. Teva has argued that such extensive assistance from foreign lawyers has not been necessary and that these costs are not "necessary costs incurred in relation to the action" within the meaning of Section 20-5, Sub-section 1, of the Civil Procedure Act.

Attorney Stenvik has maintained this legal cost claim in a letter of 17 March 2023. He has noted, in this regard, that the law firm of WilmerHale has gained an in-depth understanding of the issues raised by the case and has a comprehensive overview of the facts of the case and the relevant technical documentation, and that the costs included in the legal cost claim only pertain to work on the action in Norway. Furthermore, he has noted that the legal fee claim of BMS includes 331 fewer hours of work (at that point in time) than has been billed by counsel to Teva, and that this would not have been possible without the contributions from WilmerHale.

The relevant issue is what can be considered "necessary costs incurred in relation to the action", cf. Section 20-5 of the Civil Procedure Act. In assessing this, weight shall be attached to whether it was reasonable to incur such costs in view of the importance of the case. It is a prerequisite that the work in question has benefited the case. The Court will proceed on the understanding that these expenses only relate to work on the present case, as stated by Attorney Stenvik. Furthermore, the Court has attached weight to BMS having claimed legal fees in respect of more than 300 fewer hours of work than has been billed by counsel to Teva,
and that this has been possible because of the assistance from the law firm of WilmerHale. Based on an overall assessment, which also takes into account the amount of the opponent's total legal cost claim, the Court finds that the costs claimed have been necessary and, having regard to the importance of the case, reasonable.
The amounts are exclusive of Value Added Tax, as the latter is not claimed. The Court accepts the legal cost specification.

Since both parties have moved for the Court to appoint expert lay judges, they are liable for half of the total costs associated therewith in relation to each other, but are jointly and severally liable for the full amount of such costs in relation to the public administration, cf. Section 2 of the Court Fees Act. Since BMS has prevailed in the case, the Court has concluded that Teva shall compensate BMS for its share of these costs. The amount of the costs associated with the expert lay judges will be determined in a separate ruling after the present judgment has been delivered.

The court fees shall be paid by the party that did not prevail in the case, in accordance with an invoice to be issued by the Court.

This judgment is unanimous.

CONCLUSION OF THE JUDGMENT

1. The Court finds in favour of Bristol-Myers Squibb Holdings Ireland Unlimited Company.

2. Teva Pharmaceutical Industries Ltd and Teva Norway AS are ordered to pay, jointly and severally, the legal costs of Bristol-Myers Squibb Holdings Ireland Unlimited Company in the amount of 9,555,655 - nine million five hundred and fifty five thousand six hundred and fifty five - Norwegian kroner within 2 - two - weeks of service of this judgment.

3. In addition, Teva Pharmaceutical Industries Ltd. and Teva Norway AS are ordered to pay, jointly and severally, the share of the costs associated with the expert lay judges for which Bristol- Myers Squibb Holdings Ireland Unlimited Company is liable. The amount of such costs is to be established in a separate order.

Court adjourned

Torild Margrethe Brende

I confirm that the other members of the Court have approved the contents of this ruling by e-mails of 16 and 21 May 2023, respectively, cf. Section 4, Sub-Sections 2 and 3, of the Signature Regulations.

Torild Margrethe Brende

Guidance notes on the right of appeal in civil actions are appended

APPENDIX 19

Translation of Swedish Judgment

Teva Sweden Aktiebolag v. *BMS Holdings Ireland Unlimited Company*,
2nd November 2022

JUDGMENT
1.The Patent and Market Court dismisses the claim.
2.The Patent And Market Court orders Teva Sweden Aktiebolag to reimburse Bristol-Myers Squibb Holdings Ireland Unlimited Company USD 1,571,287.25, EUR 118,657, GBP 56,382 and SEK 292,652 for its legal costs, of which USD 1,200,000 relates to fees, USD 45,000 to own work and USD 326,287.25, EUR 118,657, GBP 56,382 and SEK 292,652 to disbursements, plus interest in accordance with Section 6 of the Swedish Interest Act (1975:635) from the date of this judgment until payment is made.

BACKGROUND
Bristol-Myers Squibb Holdings Ireland Unlimited Company (BMS Holdings) and Teva Sweden Ak:tiebolag (Teva) are two companies active in the pharmaceutical industry. BMS Holdings supplies a medicinal product used in the treatment of thromboembolic disorders i.e. to prevent blood clots from blocking blood vessels. The medicinal product contains an inhibitor of an enzyme called factor Xa (fXa), which is involved in the blood clotting process.
Following an assignment from Bristol-Myers Squibb Company (BMS Company), BMS Holdings is the holder of European patent EP 1 427 415 (the Patent). The Patent, which has been validated in Sweden, is entitled 'Laktam-innehallande foreningar och derivat darav sasom faktor Xa-hammare' [Lactarn-containing compounds and derivatives thereof such as factor Xa inhibitors] in the Swedish translation.
The patent is based on international application PCT/US2002/029491 (the PCT Application) filed by BMS Company on 17 September 2002. The application, which was assigned publication number WO 03/026652 (WO 652), claimed priority from the US application US 60/324 165 (US 165) filed by the inventors Donald J. Pinto and Mimi L. Quan on 21 September 2001. The PCT Application was later completed at the European Patent Office (EPO), where it was assigned application number 02775843.2.
Claim 1 has the following wording in the Swedish translation:
Forening vilken representeras av formel (I):

[Diagram not included in judgment]

eller ett farmaceutiskt godtagbart salt darav [A compound represented by the formula (1): or a pharmaceutically acceptable salt thereof].
Claim 7 has the following wording in the Swedish translation:
Forening enligt patentkrav I eller 2, for anvandning vid behandling av en tromboembolisk storning [A compound according to claim 1 or 2, for use in the treatment of a thromboembolic disorder].
The compound in claim 1 is a medicinal substance that has been given the internationally accepted generic name (also called the INN name, short for International Nonproprietary Name) apixaban by the World Health Organization.
BMS Holdings is also the holder of the Swedish supplementary protection certificate SE 1190029-7 for the product 'Apixaban and pharmaceutically acceptable salts thereof' which has the Patent as its basic patent.
In June 2021, Teva brought an action against BMS Holdings for invalidity of both the Patent and the SPC. Teva's action covers issues which, in addition to the above claims, relate to claims 3-6 and 8-29, which have the wording set out in Appendix 1 in the Swedish translation.

CLAIMS, ETC.
Teva has claimed that European patent EP I 427 415 be declared invalid in Sweden.
Teva has also claimed that SPC SE 1190029-7 be declared invalid
BMS Holdings has contested these claims.
The parties have claimed reimbursement of legal costs.

GROUNDS
Teva
The Patent is not entitled to priority from US 165. The invention lacks novelty over the state of the art at the filing date. It also lacks any inventive step in relation to the state of the art at the priority date. The Patent comprises an element that was not specified in the application at the filing date. A person skilled in the art lacks the necessary instructions to realise the invention in its full scope.
The patent underlying the SPC is invalid. The product to which the SPC relates was developed after the date of the patent application.
Teva is prejudiced by the Patent as the company is excluded from a potentially relevant market.
BMS Holdings
The priority date of the Patent is 21 September 2001. Patent application WO 03/049681 (WO 681) was filed after this date. The novelty requirement is met.
The invention in the patent - apixaban - solves the objective technical problem and the technical effect was rendered probable at the time of the application. At that time, it was also rendered probable that apixaban could be used as a medicinal product to treat thromboembolic disorders.
The invention possesses inventive step. A person skilled in the art would not arrive at apixaban on the basis of WO 00/39131 (WO 131), which is the closest prior art. A person skilled in the art would not have combined WO 131 and WO 01/47919 (WO 919). Even if a person skilled in the art had done so, they would not have arrived at apixaban.
A person skilled in the art can realise the invention according to the Patent. The Patent does not comprise an element that was not specified in the application at the Apixaban is protected by a basic patent in force within the meaning of Article 3(a) of Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products (the SPC Regulation). Apixaban was not developed after the priority date or the filing date.

DEVELOPMENT OF THE CLAIM

Teva

A person skilled in the art
A person skilled in the art is a group of specialists consisting of a medicinal chemist, a pharmacologist and a clinician working primarily on cardiovascular diseases. The medicinal chemist has knowledge of the preparation of drug candidates from known active compounds and from studies of the structural and activity relationships of groups of compounds. They also have knowledge of properties such as solubility, bioavailability and selectivity. The pharmacologist, who has knowledge of target receptors to which drug candidates can bind, is well versed in performing in vitro and in vivo studies to analyse affinity and selectivity for a given target receptor. The clinician has good experience of medicinal products to treat, among other things, conditions that may be caused by thromboembolism. Furthermore the clinician has knowledge of how clinical trials are conducted.

Novelty
The Patent is not entitled to priority from US 165. Even if the inventors Donald J. Pinto and Mimi L. Quan were to be deemed to have assigned the rights to said application to Bristol-Myers Squibb Pharma Company (BMS Pharma) on 3 November 2001, as alleged by BMS Holdings, there is no evidence that

BMS Pharma subsequently assigned the rights to BMS Company before the latter company filed WO 652 on 17 September 2002.
The question of priority is to be decided on the basis of Article 87 of the European Patent Convention (EPC). It follows from this provision and from EPO practice that associated companies must be treated as separate entities, that the right to claim priority must have been assigned during the priority year and that it must be very clear both that the parties have entered into an agreement and what the agreement contains.
If the court were to find that US law is to be applied, it is federal law that is at issue, not Delaware state law. Federal law states that an assignment must be in writing. The provision of Section 261 of 35 U.S.C. has the following wording: 'Applications for patent, patents or any interests therein shall be assignable in law by an instrument in writing'. The requirement for the written form also applies between parent companies and subsidiaries.
A consequence of BMS Holdings not being entitled to claim priority from US 165 is that the Patent lacks novelty in relation to WO 681 filed on 3 December 2002, in which priority is claimed from US patent application US 60/339,085 (US 085) filed on 10 December 2001. In compound 62 on p. 56 and in example 53 on p. 105 of WO 681, apixaban is described as an individualised compound. The fact that the compounds described in WO 681 are intended to be used in therapeutic applications is already evident from the fact that the compounds are to be used as inhibitors of factor Xa.

Inventive step

Closest prior art, etc.
WO I 31 relates to the same purpose as the Patent, i.e. to treat thromboembolic disorders by inhibiting fXa with heterobicycles. Claim 1 of WO 131 relates in part to compounds with the structural formula set out below.

[Diagram not included in judgment]

Apixaban, i.e. 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidine-1-yl) phenyl-4,5,6,7- tetrahydro-1 H-pyrazolo [3,4-c] pyridine-3-carboxamide, is described generically in WO 13 I and thus falls within the scope of protection applied for in the application. The specific heterobicycle tetrahydro-1 H-pyrazolo[3,4-c] pyridine is explicitly described.WO 131 describes three of the four groups on the heterobicycle as preferred and exemplifies them specifically. In addition, a number of specific examples of how these groups can be combined are described.
The only possible difference between WO 131 and claim 1 of the Patent is that WO 131 does not explicitly exemplify the choice of oxopiperidinyl, i.e. a lactam ring, as the B group on the heterobicycle.
The invention demonstrates no technical effects
The technical effect was not rendered probable at the time of filing the patent application and should therefore be disregarded when assessing inventive step.
The WO 652 application covers a very large number of compounds. It does not contain any biological data, only assumptions that the compounds described would be useful as anticoagulants.
In WO 652, the invention was defined as the lactam-containing compounds according to formula I (P4-P-M-M4), or stereoisomers or a pharmaceutically acceptable salt thereof. With a large number of options for each of P4, P M and M4 the description covers an essentially unlimited number of compounds. Even the preferred embodiments are essentially unlimited in number as they involve a large number of variations of compounds with different structural properties without providing any guidance as to which compounds inhibit fXa. WO 652 is based on the assumption that the compounds described are useful as anticoagulants and expresses it as 'The anticoagulant effect of the compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin'. Therefore, the inventors did not even know what was the target that had to be affected to achieve the desired inhibitory effect, which underlines the speculative nature of the patent. In addition to fXa, WO 652 lists potential inhibition of other serine proteases. Some of these are procoagulant factors and their inhibition may result in an

anticoagulant effect, while others may promote the stabilisation of blood clots and therefore have the opposite effect to an anticoagulant.
The application describes an in vitro test to measure inhibition of fXa using the dissociation constant Ki. The test was well known to a person skilled in the art on the filing date. There is no information on which of all the compounds covered by WO 652 was/were tested according to the test described or which exhibited Ki values of ≤10 µM. Consequently it is not clear which Ki values were achieved for a specific compound or even why a value of ≤ 10 µM would be deemed to confirm the usefulness of the compounds as effective inhibitors of fXa. In addition, a Ki value of ≤ 10 µM was not sufficient for an fXa inhibitor to be deemed useful as an anticoagulant. Therefore, the mere claim of a Ki value of ≤ 10 µM would not lead a person skilled in the art to conclude that a particular compound exhibits relevant biological activity against fXa, let alone that it has anticoagulant activity in the blood or that it is potentially suitable as a medicinal product.
The animal experiment described in WO 652 represented a standard method for assessing anticoagulant activity in vivo**.** However WO 652 does not contain any data from animal experiments showing anti-thrombotic effect for any of the compounds in question or even an indication that any such experiments had been carried out.
The patent contains 140 examples of syntheses of compounds, but no biological data at all to support the effects that the invention is claimed to exhibit. The patent only describes the properties that it would have been desirable for the compounds to exhibit. These properties are general and it was part of the general knowledge of a person skilled in the art that potent and specific fXa inhibitors could be useful for the treatment of thromboembolic disorders, for which reason this cannot be a contribution to the state of the art
A person skilled in the art would have no reason to believe that a specific compound in the patent would exhibit any effect as an fXa inhibitor and, in particular, would not exhibit any additional effects beyond those already described in WO 131.
The difference between the patent and WO 131, i.e. the use of a lactam ring as a B group, does not entail any demonstrated technical effect, let alone an improved effect.
Data published subsequently
Since the alleged effect has not been rendered probable by the application, data published subsequently should not be taken into account. In the event that such data is taken into account anyway, in assessing whether the effect has been rendered probable, it is necessary to take into account the fact that there are also tests published in articles in 2006 and 2007 showing that compounds similar to apixaban, but with a functional group other than a lactam group as the B group, exhibit the same Ki value as apixaban or a lower Ki value. This applies, for example, to compounds that are structured in the same way as example 1053, example 221 and example 86 in WO 131. In the tests, it has been shown that such compounds have a Ki value of 0.00007 µM, 0.00018 µM and 0.00004 µM, respectively, which should be compared to apixaban which has been stated to exhibit a Ki value equivalent to 0.00008 µM. Consequently, there are compounds in WO 131 that are not only comparable to apixaban, but also superior to apixaban in terms of affinity to fXa. No technical effect can therefore be attributed to the choice of the lactam group even in the light of data published subsequently.

The objective technical problem
It has not been rendered probable in either WO 131 or WO 652 that any of the compounds described is an fXa inhibitor.
However, if this is in fact deemed to have been rendered probable, the objective technical problem should be formulated as the provision of an alternative compound that inhibits fXa. This is in view of the fact that it has not been rendered probable, either in the application as submitted or in the light of data published subsequently, that the compounds in the application have been improved in comparison with those in the closest prior art.
The solution to the problem was obvious to a person skilled in the art
The difference between WO 131 and claim 1 of the Patent is at most that the compound in claim 1 includes a lactam group. Since lactam groups are common in medicinal chemistry, such a group would

constitute an alternative B group for a person skilled in the art in the type of compound described in WO 131.
WO 919 describes fXa inhibitors with a different core structure, but with similar substituents in positions similar to those in claim 1 of the Patent. One of the substituents in WO 919 with particularly good affinity is an oxopiperidinyl in the corresponding position to that in apixaban exemplified in example 129, among other things. A person skilled in the art who, starting with WO 131, was looking for an alternative fXa inhibitor, would thus, on the basis of WO 919, have found reason to use an oxopiperidinyl as B group. This solution was obvious to a person skilled in the art.

The invention comprises an element that was not specified in the patent application at the filing date
No guidance is given in WO 652 that allows a person skilled in the art to understand why apixaban in particular should be selected from the essentially unlimited number of compounds proposed. There is also no information to support apixaban as a factor Xa inhibitor and in particular as an improved factor Xa inhibitor. Therefore, when the patent application was limited to comprise only the compound apixaban, a person skilled in the art was faced with new technical information that did not exist on the filing date, because it meant that apixaban thus assumed a unique position.

There are insufficient instructions to realise the invention
A person skilled in the art is not given sufficient guidance on how to obtain a pharmaceutically acceptable salt of apixaban. The Patent does not disclose any specific salts of apixaban. The compound does not include any groups that can easily absorb or release a proton. Moreover, it is essentially impossible to predict whether a potential salt would be pharmaceutically acceptable.
A person skilled in the art is also not given sufficient guidance on how apixaban could be used in medical treatment. The potential use of an fXa inhibitor to treat a thromboembolic disorder, which the patent description refers to and which, in the case of apixaban, is described in claim 7, among other things, was based solely on an assumption. WO 652 lacks relevant biological data for it to have been rendered probable that any compound in it was useful, or potentially useful, in treating thromboembolic disorders. Nor did anything else in the description provide guidance as to how the compounds in WO 652 could give rise to a technical effect. The general medical effects in claims 5-6 and the specific medical effects in claims 7-29 were not rendered probable at the filing date. The deficiencies in the description are so substantial that a person skilled in the art cannot realise the invention.

Supplementary protection certificate
At the filing date, BMS Company had listed only an essentially unlimited number of compounds. Although apixaban falls within the general definition of formula I (P_4- P-M- M_4) in WO 652, which is known as a Markush structure, i.e. structural formulae of chemical compounds represented with variable groups, the usefulness of the product, the active substance apixaban, was discovered through research projects conducted several years after the filing date. It is irrelevant that apixaban may have been synthesised at an earlier date.

BMS Holdings

A person skilled in the art
A person skilled in the art consists of a group of people with expertise in medicinal chemistry, biology and/or biochemistry, pharmacology and pharmacokinetics. The group has relevant experience in metabolism, toxicology, formulation and clinical medicine. The group also has specific experience of the design, synthesis and purification of pharmaceutical compounds.
The medicinal chemist in the group is a chemistry graduate with a PhD and/or several years of experience of medicinal product development in the pharmaceutical industry. The clinician/pharmacologist who is also part of the group has a medical degree with specialisation in cardiology and either a PhD combined with one year of experience or three years of experience of randomized clinical trials and medicinal product development. The clinician/*pharmacologist has*

written a large number of scientific articles and their knowledge covers pharmacology and thrombotic mechanisms at the preclinical and clinical levels. The pharmacokineticist who is also in the group has either a PhD in pharmacokinetics and one year of experience of assessing the pharmacokinetic properties of small molecules or a Master's degree in the same field and three years of experience of the same type of assessment. The pharmacokineticist has in-depth knowledge of all aspects of absorption, distribution, metabolism and excretion of medicinal products.

Novelty

The right of priority was created to protect the person entitled to the priority, i.e. the applicant or the person who has taken over the applicant's rights. It was not created for the purpose of protecting third parties. Instead, the interest of third parties is served by the requirement that the same invention must be involved for an applicant, or the person who has taken over the applicant s rights, to claim priority. As a third party, Teva has no legitimate interest in relation to priority.

Notwithstanding this BMS Company has been entitled to claim priority based on US 165. Article 87 of EPC does not set out any specific requirements for what is required for someone to have taken over the applicant's rights. This issue is instead governed by national law.

The inventors of the patent were employees of DuPont Pharmaceuticals Company (DuPont Pharma) when US 165 was filed. On 1 October 2001 BMS Company's wholly owned subsidiary E.R. Squibb & Sons LLC (Squibb & Sons) acquired 50 per cent of DuPont Pharma. At the same time, Squibb & Sons' wholly owned subsidiary Bristol- Myers Squibb Pharma Holding Company acquired the remaining 50 per cent of DuPont Pharma. In connection with the acquisitions, DuPont Pharma changed its name to BMS Pharma.

[Diagram not included in judgment]

In US law, which is divided into federal law and state law, ownership of assets and construction of contracts are governed by state law. This also applies to patents. BMS Company and the above-mentioned subsidiaries, whether owned directly or indirectly, are all incorporated in Delaware. As a result, Delaware state law applies.

Like in many other common law countries, Delaware law acknowledges that the ownership of property, both tangible and intangible, can be divided. One natural or legal person may have 'beneficial title', also called 'equitable title' to certain property while another person has 'legal title' to the same property. The beneficial owner is the holder of what is called 'beneficial title' or 'equitable title'. Under Delaware state law, the beneficial owner i.e. the holder of 'beneficial title , has the right to determine how the property in question is disposed of. The person holding 'legal title' has a duty of loyalty and care to the beneficial owner. There is no requirement for the written form for a person to be considered to be the holder of 'equitable title'.

There is no provision in federal law that would take precedence over state law regarding the existence of ownership in the form of 'legal title' and 'equitable title'.

The US Supreme Court established this as early as 1893 in the case of Dalzell v. early as 1893 in Dalzell v. Dueber Watch-Case Mfg. Co, 149 U.S. 315, 320 (1893).

It follows from the provision in Section 261 of 35 U.S.C. that patent rights may be assigned in law by means of a written instrument of assignment. The explicit reference to 'in law' makes it clear that the provision does not apply to assignments of equitable title.

Moreover, the question of ownership of patents and the above-mentioned requirement for assignment in writing are two separate issues. In *Schwendimann v. Arkwright Advanced Coating, 959 F.3d 1065 (Fed. Cir. 2020)*, decided by a federal court, it was ruled that: 'ln addition to the § 261 written instrument requirement of assignment, the plaintiff must have the legal title to the patent or patent application, which is determined by state law'.

When WO 652 was filed, BMS Pharma held the legal title and BMS Company held the beneficial title or equitable title to US 165. BMS Company's holding of beneficial title or equitable title to US 165 arises from the fact that BMS Pharma was a wholly owned subsidiary of BMS Company and there were

internal guidelines governing the holding of intangible assets within the group that were applied when WO 652 was filed. According to the guidelines, BMS Company exercised effective control over the intangible assets of BMS Pharma at that time. BMS Company's control over said assets was later confirmed in standard assignment agreements for US 165 among other things, which it entered into with BMS Pharma on 23 April 2007 and 13 December 2016. BMS Pharma had full knowledge of the relevant intra-group relationships regarding the intangible assets and the right to request priority in relation to them.
BMS Company, by virtue of being the holder of beneficial title or equitable title, is a successor in title within the meaning of Article 87 of EPC.
WO 681 has a later priority date than the filing date of US 165 and is therefore irrelevant to the question of whether the invention meets the novelty requirement.

Inventive step

Closest prior art, etc.

WO 131 describes a large number of compounds in the form of a Markush structure. Theoretically, apixaban is covered by the Markush structure, but not a single one of the 109 individually described compounds is apixaban. The specific combination of functional groups of which apixaban is composed is not indicated in any way in WO 131. The combination is not mentioned, is not represented with a structural formula and is not described in any other way. Use of the lactam contained in apixaban (2-oxo-1-piperidinyl) is not apparent from any of the examples in WO 131. Nothing is described in WO 131 that would lead a person skilled in the art to apixaban or its specific effects.
Apixaban can be divided into five structural elements:

(a) group G which is a methoxyphenyl group;
(b) group R^{13}, which is a carboxamide group;
(c) the core, consisting of a heterocyclic ring, which is a 7-oxo-4,5,6,7-tetrahydro-1H- pyrazolo-(3,4-c] pyridine group;
(d) group A, which is a phenyl group; and
(e) group B which is a 2-oxo-l-piperidinyl group, i.e. a specific lactam.
(f)

The diagram below illustrates these different structural elements of apixaban.

[Diagram not included in judgment]

Some of the compounds described in WO 131 have a similar core structure to apixaban (tetrahydropyrazolopyridinone core structure), but only four of the compounds specified in WO 131 *have more than two of the five structural elements that correspond to the specified structural elements of apixaban. These are found in examples 6, 10, 13 and 99 and are shown by the areas within the green circles below; compared to the grouping in the diagram above, they have three structural elements in common with apixaban.*

[Diagram not included in judgment]

The question of whether the invention exhibits technical effects
The technical effect achieved via apixaban compared to WO 131 is primarily an improved fXa inhibitor (lower Ki). Secondly, it is an improved fXa inhibitor (lower Ki) that also has improved pharmokinetic properties.
Via WO 652 and the general knowledge of a person skilled in the art, it was at least rendered probable to a person skilled in the art that apixaban was an improved fXa inhibitor (lower Ki) compared to the

state of the art that the compound exhibited improved pharmacokinetic properties and that it could be used as a medicinal product.
A person skilled in the art who reads WO 652 understands that the focus of the inventors was precisely fXa inhibitors. It is made clear early in WO 652 that the serine protease specifically targeted by the invention was fXa. The mechanism of action of fXa inhibitors and its effect on thrombin formation was widely accepted. The underlying aim of WO 652 was therefore to identify effective, specific fXa inhibitors. An additional aim was to provide fXa inhibitors with improved phannacokinetic properties. A person skilled in the art would have considered WO 652 in light of these underlying aims.
WO 652 describes an in vitro test of the Ki value of the compounds and how the result of said test should be evaluated. It follows from the description that a compound is deemed active if it has a Ki value ≤ 10 μM. Although it is not explicitly stated which compounds were found to have a Ki value below 10 μM, WO 652 indicates that a number of compounds were active in the test and had a Ki value ≤ 10 μM. These compounds would have been interesting for the inventors to take further for further testing.
There is also a description of an in vivo test that can be used to measure the anti- thrombotic effect of the compounds described in WO 652. It was a test with which a person skilled in the art was familiar and could perform routinely.
A person skilled in the art would have been particularly interested in the 110 compounds produced and would have found reason to analyse them further. Apixaban is one of the compounds explicitly mentioned in WO 652. The synthesis and characterisation of apixaban is described in example 18.
At the priority date, several known fXa inhibitors were already showing promising results in animal experiments and had been taken further to clinical trials. A person skilled in the art would have noted that apixaban had the same structure (P_1-core-P_4) as certain other known fXa inhibitors. Based on how fXa works in connection with the coagulation process, a person skilled in the art would further understand that by inhibiting fXa, it was possible to prevent the formation of blood clots.
Data published subsequently
Data published subsequently may be taken into account. It is not required that the technical effect of apixaban was rendered probable via WO 652 or the general knowledge of a person skilled in the art. It is sufficient that there was no reason to question the technical effect.
The fact that apixaban has a lower Ki value and improved pharmacokinetic properties is shown by data published subsequently concerning the comparative trials that have been performed showing the Ki values for apixaban and the four compounds in examples 6, 10, 13 and 99 that were known via WO 131. The examples mentioned from WO 131 represent the closest prior art. The tests show that apixaban is an improved fXa inhibitor.

The objective technical problem
Based on the difference from WO 131, the objective technical problem that the invention intends to solve must be formulated as the provision of an improved fXa inhibitor, i.e. with a lower Ki value.
Alternatively, the objective technical problem could be formulated as the provision of an improved fXa inhibitor (lower Ki) that also has improved pharmacokinetic properties.
The solution to the problem was not obvious to a person skilled in the art
WO 131 does not lead a person skilled in the art to select a lactam group as the B group or to make the other choices needed to arrive at apixaban.
The combination of properties of apixaban does not follow from WO 131; apixaban is not mentioned, is not represented with a structural formula and is not described in any other way. It takes a series of non-obvious choices, and choices that are no more obvious than other choices to arrive at apixaban from WO 131.
Using the lactam group in fXa inhibitors in the same way as in apixaban was not part of the general knowledge of a person skilled in the art at the priority date.
In order to even arrive at using a lactam group, a person skilled in the art must make a series of choices based on the general formula for the B group described in WO 131. None of the synthesised examples showed which choices needed to be made.

Furthermore, apixaban's improved Ki value is sufficient in itself to achieve inventive step. A person skilled in the art could not have predicted that the presence of a lactam group on the core structure of the tetrahydropyrazolopyridinone core would lead to improved fXa inhibitory effect compared to structurally similar compounds.
A person skilled in the art would have had no reason to combine WO 131 and WO 919. There is no reference from WO 131 to WO 919. It would only have seemed logical for a person skilled in the art to tum to WO 919 and example 129 to identify a substructure of the B group if the person skilled in the art understood that a lactam group might be appropriate as the B group on the bicyclic core of an fXa inhibitor. It was not part of the general knowledge of a person skilled in the art that lactam groups were useful in fXa inhibitors.
WO 919 shows not only the presence of lactam groups but also a large number of other substructures at different locations. To identify a lactam group as a desired structural group would therefore have required a person skilled in the art to look for that particular group. This knowledge comes from WO 652 and not from knowledge available at the filing date. The fact that lactam groups were known to a medicinal chemist does not mean that they represented an obvious alternative for a person skilled in the art. There are countless other groups, including some that are also common in medicinal chemistry, which a person skilled in the art had as much or little reason to choose.

The invention does not comprise an element that was not specified in the patent application at the filing date.
Apixaban is explicitly mentioned and described in WO 652 and, since the technical effect of apixaban was rendered probable in WO 652, the Patent does not comprise an element that was not specified in WO 652. Apixaban was one of the most preferred compounds or the most preferred compound in WO 652.

There are sufficient instructions to realise the invention
A person skilled in the art can realise the invention according to the Patent in its entire scope. Based on what is stated in paragraphs [0068]-[0069] of the Patent and their general knowledge, a person skilled in the art can produce pharmaceutically acceptable salts of apixaban by means of simple, routine work. Apixaban contains both weakly acidic and weakly basic groups. One of the nitrogen atoms in apixaban s tetrahydropyrazolopyridinone core structure can absorb a proton and the amino group of the carboxamide group can release a proton. Members of Professor Eric N. Jacobsen's research team carried out experiments in which they formed pharmaceutically acceptable salts using the functional groups contained in apixaban.
Being familiar with both the functioning of the coagulation cascade and the action of factor Xa inhibitors within it a person skilled in the art was aware that apixaban, as a specific factor Xa inhibitor, was suitable for use as an anticoagulant.

Supplementary protection certificate
It is the Patent, not WO 652, that is relevant to an assessment of whether the condition in Article 3(a) of the SPC Regulation is met. Apixaban is explicitly stated in claim 1.

THE INVESTIGATION
At Teva's request, the following witnesses have been heard as experts for the party: Dr Robert Judkins, Dr William Wargin, Dr Kim P. Gallagher, Professor Morten Gr0tli, Professor John R. Thomas and former Judge Myron T. Steele.
At the request of BMS Holdings, the following witnesses have been heard as experts for the party: Dr Robert Young, Professor David Edlinge, Professor David Taft, former Judge William B. Chandler, and Professor Emeritus Donald S. Chisum.
The parties have also relied on written evidence.

ASSESSMENT BY THE COURT

General information about the Patent

According to the description of the Patent, the invention relates to lactam-containing compounds which are inhibitors of trypsin-like serine protease enzymes, in particular fXa, and their use as anticoagulants for the treatment of thromboembolic disorders.

The description also states that activated fXa, the main practical role of which is to generate thrombin by means of limited proteolysis of prothrombin, has a central position linking the intrinsic and extrinsic activation mechanisms in the last common part of the blood clotting process. It also states that, since one molecule of fXa is estimated to be able to generate 138 molecules of thrombin, inhibition of fXa may be more effective than deactivation of thrombin in interrupting the blood clotting process.

The description explains that effective, specific inhibitors of fXa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic diseases and that it is therefore desirable to develop new fXa inhibitors.

Whether the Patent comprises an element that was not specified in the application at the filing date

According to Section 52 (1) (3) of the Swedish Patents Act (1967:837), a patent which comprises an element that was not specified in the application at the filing date must be declared invalid. The condition on support has its counterpart in Section 13 of the Swedish Patents Act, which states that a patent application may not be amended so that a patent is applied for an element that was not specified in the application at the filing date.

The fact that an amendment must be supported by the application originally filed means that the amended application must not contain information which a person skilled in the art, with reference to their general knowledge, could not directly and unambiguously, explicitly or implicitly, deduce from the application when it was filed (cf. the decision of 30 August 2011 of the Enlarged Board of Appeal of the EPO in case no. G 2/10, point 4.3).

It is undisputed that the compound to which claim 1 relates, i.e. apixaban, corresponds to example 18 (p. 220) and that the compound is also referred to on, among other things, p. 69, lines 34-36, and in claim 8 (p. 377, lines 34-36) of the originally filed application WO 652.

Apixaban is specified in the originally filed application as one of several substances that are specifically named and exemplified. According to the assessment of the Patent and Market Court, limiting an initially wider patent application to a clearly defined embodiment of the invention, in this case apixaban, does not mean that a person skilled in the art is confronted with new technical information.

The Patent therefore does not comprise an element that was not specified in the application at the filing date.

Novelty

Introduction

According to Section 52 (1) (1), cf. Section 2 of the Swedish Patents Act, a patent must be declared invalid if it has been granted for an invention which was not novel in relation to the state of the art before the filing date of the patent application.

Teva has claimed that the invention lacks novelty in relation to WO 681, filed on 3 December 2002 in which priority is claimed from US 085, filed on 10 December 2001.

The question of whether BMS Company was entitled to claim priority from US 165

Teva has claimed that BMS Company, which filed WO 652, was not entitled to claim priority from US 165 because there is no evidence that BMS Pharma assigned the rights in US 165 to BMS Company before the latter company filed WO 652 on 17 September 2002.

BMS Holdings has responded to the allegation by stating that, although BMS Pharma was the legal owner of US 165 at the time of filing of WO 652, BMS Company, as the beneficial owner of US 165 at that time, was entitled to claim priority because BMS Company was BMS Pharma's successor in title within the meaning of Article 87 of the European Patent Convention (EPC). According to BMS Holdings, the beneficial ownership of US 165 by BMS Company follows from the fact that BMS

Pharma was a wholly owned subsidiary of BMS Company, combined with the fact that, according to internal guidelines, BMS Company exercised effective control over the intangible assets of BMS Pharma when WO 652 was filed.
The Patent and Market Court will examine Teva's objection of lack of priority below, irrespective of whether it has been questioned in the context of other disputes whether a person who does not claim to have priority can succeed with such an objection (see the EPO Technical Board of Appeal's letter of 6 February 2020 for the oral hearing in case T 0419/16, paragraphs 20.4-20.5).
It follows from Article 87 of EPC that a person who has previously filed a patent application with a State or an organization bound by certain international agreements, or a successor in title, is entitled upon filing a European patent application relating to the same invention, to benefit from the priority of the earlier application for a period of 12 months from the filing date of the previous application.
First of all, the Patent and Market Court notes that, in its wording, the provision in Article 87 of EPC is not limited to situations in which the right of priority has actually been assigned. The provision merely states that a person must be the successor in title of another applicant. How this has taken place, by assignment or otherwise, is not specified. According to the Court, there is nothing to exclude the provision also being applicable where a person derives their right to claim priority from other circumstances. For example, the High Court of England and Wales (Patents Court), in a judgment of 10 July 2013 in HTC Corporation v. Gemalto S.A. et al., held that a US company (STI), in its capacity as beneficial owner of an invention which, among others, an employee and a consultant of a company in the same group (STC) developed and of which STC was the legal owner, was the successor in title of the inventors in respect of the right to claim priority from a US patent application which the inventors had filed barely a year before STI filed the patent application relevant to the case (see the judgment in joined cases HC11C01177 and HC11C01178).
In cases in which a person has claimed a right of priority as a result of an assignment by contract, the EPO has established that it is the content of national law that determines whether the right of priority has been assigned. In relation to the question of choice of law, factors such as the country in which the first application was filed, the country in which the subsequent application was filed, the national law applicable to the assignment contract and the domicile or registered office of the parties have been considered relevant (see the decision of the Technical Board of Appeal of the EPO of 9 February 2017 in T 1201/14, point 3.1.2).
The question at dispute with regard to priority is whether, during the year of priority, BMS Company was the successor in title of BMS Pharma within the meaning of Article 87 of EPC. To answer that question, the Court first needs to decide whether the inventors, who filed US 165, assigned the title to US 165 to BMS Pharma and, if so, whether BMS Company became the beneficial owner of US 165 prior to the filing of WO 652.
Considering that the inventors, BMS Pharma and BMS Company were all domiciled and had their registered offices in the United States at the time relevant in the case and that the first patent application i.e. US 165, was filed there the Patent and Market Court finds that these questions must be decided with the application of US law.
As stated in NJA 2016 p. 288 (see sections 17 and 19), it is the responsibility of the Patent and Market Court to apply and interpret the content of US law in the same way as a US court would have done.
Under US law, matters relating to contract law, including the construction of contracts, are governed by state law. The same applies to the question at issue in the case of whether someone may be deemed the beneficial owner of certain property. The fact that both the question of whether the inventors assigned the title to US 165 and the question of whether BMS Company was the beneficial owner of US 165 when WO 652 was filed have arisen as a result of Teva having questioned whether BMS Company was entitled, in WO 652, to claim priority from US l65 does not render federal law applicable to the first-mentioned questions. The Patent and Market Court did not understand the situation as being that any of the expert witnesses had suggested otherwise; it was only when they considered all the questions together that they had different views on whether state or federal law should apply.
According to the Patent and Market Court, this is confirmed by the federal court decision *in Jim Arnold Corp. v. Hydrotech Sys., Inc. 109 F.3d I 567 (Fed. Cir. 1997*), which contains the following: 'It may

seem strange at first blush that the question of whether a patent is valid and infringed ordinarily is one for federal courts, while the question of who owns the patent rights and on what terms typically is a question exclusively for state courts. Yet that long has been the law.'

Since both BMS Pharma and BMS Company are governed by Delaware law, and there is no circumstance suggesting that any other state law should apply, it is the law of that state that should be applied to the question of whether US 165 was assigned by the inventors to BMS Pharma and to the question of whether BMS Company is the beneficial owner of US 165.

US 165 was filed by the inventors Donald J. Pinto and Mimi L. Quan on 21 September 2001. The investigation in the case shows that they assigned said patent application and certain additional rights attached thereto to BMS Pharma on 3 November 2001. BMS Pharma was therefore the successor in title of the inventors in respect of US 165.

Under Delaware law, a person may be the beneficial owner of property of which someone else is the legal owner. This also applies to inventions and intellectual property rights such as patents. It follows from this law that the beneficial owner has the ultimate decision- making power over the property. No specific assignment from one owner to another is required for their different interests in the property to arise.

According to the case law of the Delaware courts, the question of whether a natural or legal person is the beneficial owner of certain property is determined based on the circumstances of each case. This is also evidenced by the case law of federal courts that have applied state law to decide such a question in the context of a case otherwise tried under federal law.

The decisions of the Delaware courts show that all circumstances are taken into account when determining whether a person is a beneficial owner and that there are no specific formal requirements. The latter courts have paid attention to the actual conduct of the persons involved and their intentions or their presumed intentions.

Teva, as the party claiming invalidity has the burden of proving that BMS Company was not entitled to claim priority from US 165. The fact that this burden was previously borne by BMS Company during the application process does not alter the assessment.

Moreover, the fact that the Patent was granted indicates that the EPO considered that BMS Company had presented sufficient evidence at that time for the EPO to disregard WO 681 in its assessment of whether the novelty requirement was met.

In addition, given that BMS Holdings provided evidence for the assessment of whether BMS Company was the beneficial owner of US 165, there is no reason to shift the burden of proof to BMS Holding on the grounds that it is easier for the latter company than for Teva to produce relevant evidence.

BMS Holdings relied, as written evidence, on a statement by Marla Mathias who, at the time of BMS Company's acquisition of the company called DuPont Pharma before the acquisition and BMS Pharma after the acquisition, was the Executive Vice President of BMS Company and its principal patent attorney. In addition, BMS Holdings relied on a written statement by Paul Golian, who was employed as an intellectual property lawyer at BMS Company in July 2002 and now holds the position previously held by Marla Mathias.

Marla Mathias' statement shows that, at the time of the acquisition of BMS Pharma, BMS Company saw no reason to become the legal owner of the intellectual property of BMS Pharma since BMS Company could in practice dispose of it in the way it wished.

Paul Golian's statement shows that his experience during the 20 years he has worked at BMS Company is that it is BMS Company that has made the decisions on how to dispose of the intellectual property rights, both those held by the company and those held by its wholly owned subsidiaries. According to him, decisions are typically made by the company's intellectual property lawyers, who often consult people in both the company's tax department and its legal department before making decisions. The statement also shows that, as far as he is aware the process was the same before he started his employment and before BMS Company acquired DuPont Pharma. Finally, it appears from the statement that, since BMS Company considered that it had full control over the intellectual property rights and that it could decide whether BMS Pharma would, at a later stage, if and when necessary, assign them to BMS Company, BMS Company chose to change the name of Du.Pont Pharma to BMS Pharma instead

of transferring the rights from DuPont Pharma to BMS Company, which would have been more costly and time- consuming.
According to the Patent and Market Court, the statements by Marla Mathias and Paul Golian, which the Court finds no reason to question, show that there was a policy within the group regarding the decision-making on intellectual property rights at the time WO 652 was filed and that this policy meant that BMS Company had effective control over the rights. Taking into account the internal guidelines and the fact that BMS Pharma was a wholly-owned subsidiary, albeit indirectly owned through a subsidiary and a sub- subsidiary, of BMS Company, the Court finds that BMS Company was the beneficial owner of US 165 at the time in question.
According to the Patent and Market Court, it is also clear that BMS Company, in its capacity as beneficial owner of US 165, was the successor in title of BMS Pharma within the meaning of Article 87 of EPC when WO 652 was filed (cf. High Court of England and Wales, Patents Court judgment of IO July 2013 in the joined cases HC11C01177 and HC11C01178, HTC Corporation v. Gemalto S.A. et al., which, on the question of priority, has been referred to in Supplementary publication - Official Journal EPO 2/2015, pp. 122-123).
The Court has concluded above that BMS Company was the beneficial owner of US 165 and that it was the successor in title of BMS Pharma in respect of the possibility of claiming priority from US 165. Since the case concerns the question of whether a European patent should be declared invalid, the supplementary question, i.e. whether BMS Company as beneficial owner, was entitled to claim priority for the patent at issue here, must be decided on the basis of the provision in Article 87 of EPC, not on the basis of US law.
Teva has not claimed that BMS Company was not entitled to claim priority from US 165 because other conditions of Article 87 of EPC, such as the requirement that an application must be filed within a certain time limit, were not met.
Based on the above, it has not been shown that BMS Company was not entitled to claim priority from US 165 when WO 652 was filed.

Conclusion

In view of the fact that WO 652 claims priority from US 165, filed on 21 September 2001, and that, as stated above, the Court has not found that BMS Company was not entitled to claim priority from US 165, WO 681 did not constitute part of the state of the art when WO 652 was filed on 17 September 2002.
Since WO 681 is the only document relied on by Teva in support of its claim that the invention was not novel, the claim cannot be upheld on this ground.

Inventive step

Introduction
According to Section 2 and Section 52 (1) (1) of the Swedish Patents Act, a patent must be declared invalid if it has been granted for an invention which does not differ materially from the state of the art before the filing date of the patent application.

Closest prior art and how the invention differs from it
The invention according to claim 1 relates to the compound apixaban or a pharmaceutically acceptable salt of it.
It is undisputed that WO 131 represents the closest prior art. The difference arising in a comparison between the technical characteristics of the invention and those contained in WO 131 must be assessed on the basis of what is shown in WO 131, i.e. what can be ascertained to be known from the contents of the document.
Teva has claimed that the structural formula of apixaban is described generically in WO 131 and that the only difference is that the lactam group is not explicitly exemplified. According to the company,

WO 131 describes three of the four groups on the heterobicycle as preferred and exemplifies them specifically.
The Court notes first of all that the specific heterobicycle contained in apixaban is not specified as preferred in WO 131, but must be selected from a number of such heterobicycles. A combination of other apixaban substituents is not specified as preferred in WO 131 either.
In its assessment of what constitutes the difference between the invention according to the patent and the content of WO 131, the Court finds that, according to practice, a specific combination of elements is novel and therefore not previously known where selection from several lists is required to achieve the combination, (cf. the decision of the Technical Board of Appeal of the EPO in T 12/81, Case Law of the Boards of Appeal of the European Patent Office 10th ed. 2022, section I.C.6.2). Therefore, on the basis of the generic formulae a person skilled in the art would not have arrived at the difference claimed by Teva.
Of the compounds specifically mentioned or produced in WO 131, apixaban differs from each of them in at least two positions. Four of the compounds (examples 6, 10, 13 and 99) exhibit the most structural similarities, i.e. from them a minimum of structural modifications are required to arrive at apixaban.
Apixaban differs from all of these examples in having a lactam group as the B group and, in addition, apixaban has a different heterobicycle from the compounds in examples 6, 10 and 13. In example 99 the heterobicycle is the same, but apixaban has a carboxamide group in the position where example 99 has trifluoromethyl.

The question of whether the invention exhibits technical effects
Teva has claimed that, at the time of filing of the patent application, it was not rendered probable that apixaban had any effect as an fXa inhibitor and that, even if it did, it was not rendered probable that apixaban had an improved technical effect compared to other fXa inhibitors in WO 131. Teva has argued in this respect that WO 652 comprises a very large number of compounds and that the application does not contain any biological data, only assumptions that the compounds described were useful as anticoagulants.
The Patent and Market Court finds first of all that the technical effect must be deducible from the patent application, either directly or via the general knowledge of a person skilled in the art.
The patent description specifies that the invention relates to lactam-containing compounds which are inhibitors of trypsin-like serine protease enzymes, in particular fXa, and their use as anticoagulants in connection with the treatment of thromboembolic disorders. Furthermore, it is stated that there is a need for effective, specific inhibitors of fXa as potentially useful active substances for the treatment of thromboembolic diseases. Against this background, it is stated that the discovery of new fXa inhibitors is desirable, which is therefore the technical problem that the patent intends to solve. The compound apixaban (or a pharmaceutically acceptable salt of it) is specified as a solution to the problem in accordance with claim 1.
The question here is how a person skilled in the art, given their general knowledge, perceived the content of the patent specification on the priority date and whether they would have found that apixaban could provide a solution to the problem posed in the patent specification. In this context, a person skilled in the art may be said to have had knowledge of the processes in the field of medicinal product development involving the preparation of drug candidates equivalent to the knowledge of a medicinal chemist, as well as knowledge of how a proposed medicinal substance is evaluated in terms of its properties. This included knowledge in the fields of pharmacokinetics and pharmacology.
The background to the patent specification describes some previously known fXa inhibitors. For example, WO 131 is mentioned in paragraph [0007]. It is further stated that the object of the invention is to provide compounds which are fXa inhibitors and thus useful for preventing blood clotting.
Pages 83-84 contain a description of how tests were carried out to establish the effectiveness of the compounds. These tests were carried out as in vitro tests and it is stated, without further specification, that a number of the compounds exhibited Ki values of $\leq$10 μM.
Paragraph [0116] further state that compounds need to have a value of $\leq$10 μM to be deemed active and preferably a value of ≤ 0.001 μM. Finally, the paragraph states that the testing showed that a number

of compounds had values of ≤10 μM, which is stated to have confirmed their usefulness as effective fXa inhibitors.
In the following paragraph [0117], reference is made to the fact that the antithrombotic effect may be demonstrated via experiments on rabbits (rabbit arterio-venous (AV) shunt thrombosis model).
The investigation in the case shows that, on the priority date, a person skilled in the art was aware of the process of medicinal product development involving preclinical research with in vitro tests of the affinity of a drug candidate to a target enzyme. This included knowledge of the generation and analysis of Ki values and further evaluation of relevant drug candidates in subsequent animal experiments.
At the priority date the general knowledge of a person skilled in the art also included an understanding of the mechanisms that regulate blood clotting through the coagulation cascade. This describes the series of reactions in which proteins in the blood are activated in sequence to form fibrin platelets to which red blood cells adhere. A person skilled in the art also knew where in the coagulation cascade fXa performed its function. See the figure below.

[Diagram not included in judgment]

A person skilled in the art had knowledge of the binding sites S_1 and S_4, which are sites on the fXa enzyme that bind substances that act on the enzyme (cf. for example: 'The Use of 3D Structural Data in the Design of Specific Factor Xa Inhibitors', Maignan S. et al., Current Topics in Medicinal Chemistry 2001, I, 161-174, and 'Annual reports in Medicinal Chemistry', 34, 9, 81-100, Fevig J.M. & Wexler R.R., Chapter 9. Anticoagulants: Thrombin and Factor Xa inhibitors, 1999, Academic Press).
Furthermore, a person skilled in the art was aware of the characteristics necessary for a potentially useful fXa inhibitor and that a number of fXa inhibitors had undergone extensive preclinical tests on animals, as confirmed by data provided by Dr. Gallagher.
The Court notes that the Patent describes experiments that have been carried out, but that there is no mention of specific biological data. However, in practice, there is no absolute requirement that experimental data be disclosed in a patent (or in a patent application). In some cases, a mechanistic explanation or the general knowledge of a person skilled in the art may be sufficient (see EPO Technical Board of Appeal decisions in T 578/06 and T 1322/17, Case Law, section I.D.4.3.3).
In the assessment now to be made, the Court finds that a person skilled in the art had knowledge of the enzyme fXa and that this could be inhibited. They also had knowledge of the role of the enzyme in the coagulation cascade. A person skilled in the art also knew how fXa inhibitors bind to the enzyme and that substances with effect as fXa inhibitors were useful as anticoagulants.
A person skilled in the art was also knowledgeable about the processes of medicinal product development in general and, in particular, the testing of a potential drug candidate that needed to be done at an early stage to determine, among other things, its affinity.
The expert witnesses relied upon by Teva have confirmed that a person skilled in the art was knowledgeable in the technical field of fXa inhibitors and was able to investigate both affinity values and pharmacokinetic parameters using routine methods.
According to the Court, a person skilled in the art who, with their general knowledge, studied the patent specification would consider it probable that apixaban was an fXa inhibitor and, in the absence of any indication to the contrary, would not have found grounds for doubt. The mere absence of specific biological data would not have led a person skilled in the art to question the function of apixaban, nor has the investigation in the case revealed anything else that would have given a person skilled in the art reason to doubt the function of the compound as an fXa inhibitor.
The application therefore rendered it probable that apixaban was an fXa inhibitor. It follows from this that a person skilled in the art, with their general knowledge, recognised the potential suitability of the compound for use as an anticoagulant.
Teva has also claimed that the Ki value of ≤10 μM specified in the Patent is not sufficient for a given compound to exhibit relevant biological activity let alone to have anticoagulant activity in the blood or for a compound with such a Ki value to be potentially suitable as a medicinal product.

The Court notes first of all that Teva has merely pointed to the fact that there is no biological data in the patent, but that it has not presented any evidence to support the view that a person skilled in the art who, as stated above, recognised that apixaban was an fXa inhibitor, would have reason to doubt the usefulness of apixaban.
A person skilled in the art, recognising that apixaban was an fXa inhibitor, would have realised its potential suitability in connection with the treatment of thromboembolic disorders. This could have been confirmed via the routine experiments specified in the patent specification.
On the basis of the above, the Patent and Market Court finds that the problem posed in the Patent has been solved, i.e. the provision of a new fXa inhibitor which is active as an anticoagulant and potentially useful as an active substance for the treatment of thromboembolic disorders.

The objective technical problem
The Court has concluded above that the problem as formulated in the Patent may be considered to have been solved.
The objective problem faced by a person skilled in the art should thus be formulated as the provision of an alternative fXa inhibitor, active as an anticoagulant and potentially useful as an active substance for the treatment of thromboembolic disorders.

The question of whether the solution to the problem was obvious to a person skilled in the art
The question that the Court must first consider is whether, based on the content of WO 131, a person skilled in the art would have arrived at the invention in accordance with the Patent.
Teva has claimed that the only difference between the Patent and WO 131 is that apixaban includes a lactam group and that the choice of such a group as the B group was obvious to a person skilled in the art, who would therefore have tested such a group as an alternative.
Based on the structurally closest compounds shown in examples 6, 10, 13 and 99 (separately) in WO 131, a person skilled in the art needed to make several independent choices to arrive at apixaban. Example 99 is the only example that shows the same core structure, but apixaban differs both in terms of the lactam group (which is aminomethyl in example 99) and the carboxamide group (which is trifluoromethyl). A person skilled in the art would therefore not have arrived at the invention according to claim 1 from the closest prior art in WO 131 without guidance.
Teva has also pointed out that lactam groups are common in medicinal chemistry.
Professor Grøtli has stated in his opinion that 2-oxo-1-piperidinyl groups are a structural design which, at the time of the priority application, was common in certain bioactive molecules in medicinal chemistry, and the interview with him revealed that this had subsequently been confirmed when he had carried out a database search in the time after he had submitted his written opinion. However, there is no investigation in the case regarding said database search.
Dr. Judkins has stated that a medicinal chemist, with the knowledge of fXa available, and known fXa inhibitors such as DPC423, would have considered it probable that a lactam group would bind to the S4 site on the fXa enzyme and also that a distal lactam group such as in apixaban constitutes a possible isostere for the distal aromatic part in DPC423.

[Diagram not included in judgment]

Taking into account Dr. Judkins' opinion about the isosteric nature of the lactam group, the Court finds that a person skilled in the art knew the concept of bioisosterism, which includes the knowledge that certain chemical groups with similar properties are interchangeable in pharmaceutical compounds.
However, in the opinion of the Court, Teva has not shown, on the basis of the information set out above, that the lactam group was common in medicinal chemistry at the time relevant in the case. It has not been made clear that the group belonged to the general knowledge of a person skilled in the art in the technical field, nor has the investigation in the case shown that a lactam group was a bioisostere known to a person skilled in the art that would be an obvious alternative in the relevant technical field.

It follows from this that the lactam group was not a chemical group that a person skilled in the art would have considered using.
In addition to what was stated above, a person skilled in the art proceeding from the content of WO 131 would also have needed an instruction that the B group in particular should be modified, and no such instruction bas been demonstrated.
It has therefore not been shown how a person skilled in the art, on the basis of the content of WO 131 with their general knowledge, would have been guided to substitute the known compounds in WO 131 with a lactam group in the position in question and thus have structurally approximated the structure of apixaban.
In conclusion, it is the assessment of the Court that a person skilled in the art, with their general knowledge, based on the content of WO 131 and faced with the problem of developing an alternative fXa inhibitor, active as an anticoagulant and potentially useful as an active substance for the treatment of thromboembolic disorders, would not have arrived at the invention according to claim 1.
Finally, the Court has to decide whether a person skilled in the art, based on the content of WO 131 in combination with what is known via WO 919, would have arrived at the invention according to the patent.
Teva has claimed that, based on the art in WO 919, a person skilled in the art would have been guided to use an oxopiperidinyl group as the B group. Teva has pointed out that one of the substituents which confers particularly good affinity is an oxopiperidinyl in the position corresponding to that in apixaban (example 129) and that a person skilled in the art would therefore have found a reason to use such a group as a substituent.
The Court finds that from the data presented in WO 919 it is not possible to link the affinity values reported to any specific substituent. It is also not clear from WO 919 how a lactam group would affect the pharmacological profile in the technical field in question. WO 919 shows compounds that are structurally different from those in WO 131 in terms of both their core structure and the substituents in the molecule as a whole. In addition, WO 919 suggests a large number of possible substituents for a person skilled in the art to choose from.
Therefore, a person skilled in the art would not have found any instruction that would have led to a lactam group being tested.
In addition to the choice of a lactam group in the position in question, a person skilled in the art would also have needed to make another structural change to arrive at apixaban.
Therefore, a person skilled in the art who proceeded from WO 131 would not have arrived at the invention on the basis of WO 919 either.
The product claims 3-4 and the therapeutic use according to claims 5-29 involve the compound apixaban and, for the same reasons as above, these claims thus exhibit inventive step.
Overall, the Court finds that the invention according to claims 1 and 3-29 differs materially from the prior art in WO 131, and the prior art in WO 131 in combination with WO 919.

Data published subsequently
The Patent and Market Court has concluded above that the invention according to the patent exhibits inventive step and, on this basis, the data published subsequently is irrelevant.
Whether there are sufficient instructions to realise the invention
According to Section 52 (1) (2) of the Swedish Patents Act, a patent must be declared invalid if it relates to an invention which is not so clearly described that a person skilled in the art can realise the invention on the basis of the description. A person skilled in the art makes their assessment based on the patent as a whole and in light of their general knowledge (cf. Case Law, p. 382, Section II.C.4.1 and the practice cited there).
Teva has claimed that a person skilled in the art is not given sufficient guidance on how to obtain a pharmaceutically acceptable salt of apixaban and the same applies to how apixaban can be used in medical treatment.
The Patent and Market Court notes first of all that paragraphs [0068]-[0069] of the Patent describe suitable pharmaceutically acceptable salts and that they can be produced by means of conventional

chemical methods. Professor Eric N. Jacobsen's expert opinion shows that pharmaceutically acceptable salts of apixaban can be produced by means of conventional chemical methods, which Teva has not contested. In the Court's opinion, the aforementioned paragraphs, in combination with the general knowledge of a person skilled in the art, therefore provide sufficient guidance for a person skilled in the art to be able to create pharmaceutically acceptable salts of apixaban.
Claims 5-6 and 7-29 cover the use of apixaban (or compositions of it) according to the first and second medical indications, respectively. The Patent and Market Court has already concluded above that it has been rendered probable in the Patent that apixaban is a factor Xa inhibitor and that the compound is potentially suitable for use in connection with the treatment of thromboembolic disorders. Consequently, based on their general knowledge and guided by the description of the Patent, a person skilled in the art could provide and use apixaban for these purposes (cf. Case Law, p. 420, Section II.C.7.2).
The Court's assessment is therefore that the invention is so clearly described that a person skilled in the art could, guided by the description, realise the invention as it is specified in the claims.
Supplementary protection certificate
The provisions on invalidity of a supplementary protection certificate are contained in Article 15 of Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products (the SPC Regulation). Article 15(1)(a) provides that a supplementary protection certificate must be declared invalid if it was granted contrary to the provisions of Article 3 while it follows from Article l5(l)(c) that if the basic patent is declared invalid, the same also applies to the supplementary protection certificate.
Teva has claimed that the supplementary protection certificate is invalid both because the Patent is invalid and because the product apixaban was developed after the date of the application for the basic patent.
The Patent and Market Court has concluded above that the Patent is valid and therefore the claim for invalidity cannot be upheld on the first ground.
In respect of the second ground, the Court notes that claim 1 of the patent granted relates to the compound apixaban, specified by means of its structural formula. The product apixaban is therefore protected by the Patent within the meaning of Article 3(a), in the assessment of the Court. The supplementary protection certificate for apixaban was therefore not granted in breach of Article 3 and therefore Teva's claim for invalidity cannot be upheld on the second ground either.

Summary and conclusion
As stated above, Teva has not shown that the Patent comprises an element that was not specified in the application at the filing date, that there was a lack of sufficient instructions to realise the invention, or that the invention failed to meet the requirements of novelty and inventive step. Teva's claim that the Patent be declared invalid must therefore be dismissed.
Since the Patent is not invalid and it has not been shown that the supplementary protection certificate was granted in breach of Article 3 of the SPC Regulation, the claim that the supplementary protection certificate be declared invalid must also be dismissed.

Legal costs

Teva, as the unsuccessful party is ordered to reimburse BMS Holdings for its legal costs to the extent that they may be deemed reasonably necessary to look after the rights of the party (Chapter 18, Sections 1 and 8-9, of the Swedish Code of JudiciaI Procedure).
BMS Holdings has claimed reimbursement of USD 2,120,303.25, EUR 118,657, GBP 56 382 and SEK 292,652.
Of the above amounts USD 1,613 622 relates to fees, USD 45,000 to the work performed by two intellectual property lawyers at BMS Holdings and USD 461,681.25, EUR 118,657 and SEK 292,652 to disbursements.

Of the disbursements, EUR 118,657 relates to the remuneration of technical assistants USD 335,394 to the remuneration of legal representatives at a foreign law firm who have coordinated the patent disputes conducted in other parts of Europe, SEK 223,612 (211,882 + 6,116 + 5,614), USD 96,586.25 (18,930.25 + 51,606 + 26,050) and GBP 52,982 to the remuneration of expert witnesses, USD 4,193, SEK 44,040 and GBP 3,400 to remuneration for disbursements for travel and accommodation in connection with the main proceedings, USD 22,205 and SEK 25,000 to remuneration for translation and interpretation, respectively, and USD 3,303 to remuneration for courier and transport costs.

Teva has contested the reasonableness of the fees for legal representatives of USD 1,613,622, the disbursements for technical assistants of EUR 118,657, the disbursements for legal representatives at a foreign law firm of USD 335,394, the disbursements for own work of USD 45,000 and the disbursements for translation of USD 22,205.

BMS Holdings has stated that the Patent is of great importance to the company and that the case involves many complex issues, both legal and technical. The company has also stated that, since BMS Holdings is a foreign company, more work has been involved than would have been the case if it were a Swedish company. Costs for duplication of work relating to a former legal representative and a technical assistant have been deducted. The claim does not include any such costs. The company has relied on more extensive evidence than Teva, which was prompted by Teva's litigation. The disbursements for the foreign legal representatives refer to the work carried out for the Swedish proceedings. No costs from other proceedings have been passed on to this case. The costs for own work are reasonable and extremely justified. A translation agency was engaged for the translation. The price of the service was in line with the market.

Teva has stated that the claims for fees and disbursements for technical assistants and legal representatives at a foreign law firm are significantly higher than in similar cases. Although the case prompted the submission of evidence from both parties, the issues were straightforward. The case was more onerous for Teva than for BMS Holdings. Despite this, BMS Holdings is asking for more than twice as much in fees. There was a change of counsel during the proceedings, which led to duplication of work. The same applies to a technical assistant, where there was also a change during the proceedings. Costs relating to the coordination of litigation pending in other countries must not be passed on to this case, and must be reimbursed only to the extent that they are relevant to this case. In respect of the remuneration for own work of USD 45,000, this should be reduced in view of the fact that BMS Holdings had unusually extensive representation at the main proceedings, which was not necessary. Finally, translation costs of USD 22,205 seem unnecessarily high, not least in view of the limited number of opinions and the fact that the vast majority of the material was in English.

Even taking into account the importance of the dispute to BMS Holdings and its scope, the Patent and Market Court finds that the remuneration claimed for fees for legal representatives of USD 1,613,622 and the disbursements for costs of foreign lawyers of USD 335,394 is excessive. In the opinion of the Court, USD 1,200,000 and USD 200,000, respectively, must be deemed reasonable in this respect. In its assessment, the Court has taken into account the fact that the case involved many legally and technically complex issues. One of the issues that involved significant costs is whether BMS Company was entitled to claim priority from US 165. The latter issue makes this case somewhat different from other invalidity cases, in which the level of remuneration may be lower.

The Court finds that the other costs are reasonable.

On the basis of what is stated above, Teva must reimburse BMS Holdings for its legal costs as follows: USD 1,571,287.25, EUR 118,657, GBP 56 382 and SEK 292,652, of

which USD 1,200,000 relates to fees, USD 45,000 to own work and USD 326,287.25, EUR 118,657, GBP 56,382 and SEK 292,652 to disbursements.

HOW TO APPEAL**.** See Appendix 2 (PMD-02)

An appeal, addressed to the Patent and Market Court, must have been received by the Patent and Market Court no later than on 23 November 2022. Leave to appeal is required.

Peter Adamsson Ulrika Persson
Anna Hedberg Andreas Gustafsson

APPENDIX 20

Professor Morrissey's Oral Testimony in London

"*EXAMINED BY MR. PURVIS*

[This examination was confined to Prof. Morrissey confirming that the reports before the court were his and contained his own opinions, truly held, etc.]

CROSS-EXAMINED BY MR. TURNER

Q. *...I was going to start with the skilled team, if I may. Perhaps we could have a look at your report, which you probably still have with you....I want to go to paragraph 5.4....You explain in that paragraph that the synthesis of new chemical structures would be primarily of interest to the medicinal chemist. That is in the first sentence. Then, dropping halfway down, you say: 'The role of the biochemist would include performing and reviewing results of in vitro tests (such as the effects of the factor Xa inhibitors on clotting tests using citrated human plasma, as well as effects of the factor Xa inhibitors on enzymatic activity of purified factor Xa and related serine proteases) and in vivo tests (such as the AV shunt model). Then at 5.6, dropping down to the second sentence, you say: 'The biochemist would have a good working knowledge of the standard in vivo assays used to produce serine proteases inhibitors and would be able to collate and interpret results from these assays. They would also be familiar with standard animal models used to test serine protease inhibitors that targeted blood clotting enzymes, and which were promising potential clinical candidates.' You are there making the point that it is the biologist who performs the in vivo and in vitro studies. It would be the biologist, would it not, who, in the light of those assay results, and perhaps other information, would be deciding which compounds are worth carrying forward as promising clinical candidates; is that correct?*

A. *You are asking who would actually make decisions about going forward on lead compounds or promising compounds in a drug company? I think that would depend on the structure of the drug company, and who was the decision-making person.*

Q. *But it is the biological information, when you have a particular compound, I am not talking about changing the compound, if you have a particular compound and you are considering taking that forward into pre-clinical or clinical development, it is principally the biologist who is going to be interpreting the data and leading the team in deciding whether or not to take a particular compound forward into the clinic, is it not?*

A. *Well, I am a little uncomfortable with the idea of leading the team, because that would depend on the structure that the drug company had and who the decision-makers were. But I would agree that a biologist*

who oversaw these studies would give input into the interpretation of the studies and what they thought the data meant.

Q. *That biologist may have a background in biochemistry or pharmacology or a related field; is that right?*

A. *Yes.*

Q. *Pharmacology, just sort of strictly speaking, is the study of how a drug impacts the body, is it not?*

A. *Yes, the study of the interactions of drugs with the body, I agree.*

Q. *I think you refer to the skilled biologist as a biochemist and I think Dr Leadley refers to the biologist as a pharmacologist, and I am not sure that anything in this case particularly turns on that, but, strictly speaking, the person who is looking at the effect of a factor Xa inhibitor on the body is doing pharmacology, are they not?*

A. *Let me think about that for a moment. So, a pharmacologist would have a special set of skills where they know a lot about the interaction of drugs in the metabolism and those sorts of things. The blood clotting cascade is complicated, and so it is important to have someone on the team who appreciates the complexity of the blood clotting system. That can be a separate biochemist working on the team. It could also be a pharmacologist who, through years of experience, has gained knowledge of the biochemistry of the blood clotting system.*

Q. *And presumably vice versa, it may be a biochemist who has had years of exposure to pharmacology in this field?*

A. *I suppose so, yes.*

Q. *You are not a pharmacologist yourself, but I just wanted to explore with you the extent to which you understood some basic concepts in pharmacology. Some of these may seem rather trivial propositions, they are not meant to be insulting, but I need to ask them. First of all, some of these are sort of basic pharmacokinetic properties, but you are aware, presumably, that a drug which is taken orally in solid form would typically dissolve in the stomach and then be absorbed through the gut into the blood. You are familiar with that?*

A. *Yes.*

Q. *Pharmacologists often refer to the half-life of drugs. You are familiar with that as a concept, presumably?*

A. *Yes.*

Q. *A drug is cleared from the blood. After it gets absorbed into the blood, over the time it has cleared, because it has metabolised or excreted by the kidneys or both, and you are presumably familiar with this?*

A. *Yes, although there are other modes of excretion beyond just the kidneys, but yes.*

Q. *You would be familiar that for a drug to work, it needs to travel to the tissue where you want the effect, so for example if you want a drug to be effective in the brain, it needs to pass into the brain tissue; yes?*

A. *Yes.*

Q. *If you want a drug to work in the blood, you need to have sufficiently high concentrations of that drug in the blood; yes?*

A. *Yes.*

Q. *You would not dispute that anyone working in pharmacology or working on the pharmacology of factor Xa inhibitors would understand these basic principles in 2001?*

A. *I would expect them to, yes.*

Q. *Have you been involved in the development of factor Xa inhibitors for clinical use, yourself, either before September 2001 or since?*

A. *No, I have not been directly involved in the development of factor Xa inhibitors.*

Q. *Have you been involved in the development of factor Xa inhibitors for ex vivo use, such as anticoagulants?*

A. *No, not directly.*

Q. *What work had you done, if any at all, on factor Xa inhibitors by September 2001?*

A. *By September 2001? We studied the biochemical properties of blood clotting proteases, including their interactions with known inhibitors, endogenous inhibitors, et cetera. I am trying to remember if our laboratory had published anything directly on inhibition of factor Xa prior to that date. I would have to think about that.*

Q. *So leaving aside what you published, what you had actually worked on yourself, you used factor Xa inhibitors in your biochemical studies; is that correct?*

A. *I believe that is correct.*

Q. *But never from the perspective of developing a clinical compound or a compound for use commercially in any way?*

A. *That is correct.*

Q. *You say in paragraph 5.3, I do not know if you still have it open, 5.3 of your report, that the patent would be of interest to a skilled team involved in the development of factor Xa inhibitors. I think you agree that at priority date, September 2001, you did not fit that description; that is correct, is it not?*

A. *No, I was not involved in a skilled team trying to develop factor Xa inhibitors, you are correct.*

Q. *How have you attempted to put yourself into the position of such a person? You have presumably done that by reading the literature?*

A. *Yes, reading the literature, being familiar with the issues that would face a team trying to develop such inhibitors.*

Q. *And in putting yourself in that position, did you go back and review the literature prior to 2001?*

A. *Well, some of it. The literature is vast, so –*

Q. *We may discuss that a little more in due course. Factor Xa catalyses the conversion of prothrombin to thrombin, and my understanding is that the catalysis takes place in the prothrombinase complex. Could you explain to my Lord what the prothrombinase complex is?*

A. *Certainly. So, factor Xa is the active form of factor X, the catalytically active form. It is a relatively weak enzyme all by itself. It needs a protein co-factor called factor Va. When the two proteins, factor Va and factor Xa bind to each other, they create essentially a two subunit enzyme. Factor Xa is the catalytic subunit and factor Va is the regulatory subunit. Furthermore, those two proteins both bind to membranes containing phosphoserine, and so it is the complex of factor Xa and factor Va sitting on a membrane surface that represents the active prothrombinase complex. That is the complex which recognises thrombin and converts it into thrombin with relatively high efficiency.*

Q. *If I could ask you to go to L.2, tab 1. I just want to lack at the right-hand column two-thirds of the way down. Just in the middle, it says, 'In the prothrombinase complex'. Do you have that?*

A. *Yes, I do.*

Q. *'In the prothrombinase complex, the reaction rate of FXa increases 300,000-fold compared to the rate catalyzed by free FXa ...' I think, not wishing to put words in your mouth, you were explaining that factor Xa on its own does not do a great deal, but is much, much more active when it is in that prothrombinase complex, to that factor, 300,000 times more; is that what you were saying, professor?*

A. *Yes, there is a very large increase in the activity of factor Xa to cleave prothrombin to thrombin when it is in a prothrombinase complex, that is correct.*

Q. *That was well known to the skilled biologist in 2001; yes?*

A. *Yes.*

Q. *The skilled biologist would understand that if you want to use factor Xa inhibitors to decrease thrombin formation, you need your inhibitor to be effective in the prothrombinase complex?*

A. *Yes, you do.*

Q. *Because that is where the catalysis is taking place?*

A. *Let me clarify one thing; okay?*

Q. *Please do.*

A. *That is the major role of factor Xa in the clotting system. It also has some minor roles in clotting. Factor Xa can help convert factor V to Va. It is also thought to help convert factor VII to factor VIIa. It is debatable how important those roles are, but it was known that they had these minor roles. But the major role of factor Xa – and this was well known in 2000 – was activation of prothrombin to thrombin.*

Q. *I think you are agreeing with me that that takes place in the prothrombinase complex, and if you want to stop that happening, you need to have your inhibitor active in that complex?*

A. *Yes.*

Q. *I wanted just to discuss some assays with you. If you could just look at your second report....[y]ou have helpfully drawn out an assay, which I think was referred to as the chromogenic assay. Let me just explain what is going on here, and you can tell me if I have it wrong. However, this is conceptually a simple assay that takes place in the test tube, and it can measure factor Xa activity. It does that by factor Xa cleaving the synthetic substrate, and the synthetic substrate we see on the left-hand side of the drawing, and there is an arrow where factor Xa will cleave. As a result of that cleavage, there is a chromophore, which is the pNA is released and there is a colour change. So it is a measurement of factor Xa activity against a synthetic substrate. Do I have that more or less right, or please feel free to correct me?*

A. *No, that is quite correct, yes.*

Q. *The substrates that were used, we can see they appear in a lot of the papers, they were standardised, were they not? I think there is a reference in a number of the documents to S-2222, produced by Diapharma, and that was commonly used in 2001; yes?*

A. *Yes, there were multiple substrates available, but that was a very common one in measuring factor Xa prospectively.*

Q. *Presumably these were all standardised, and if you got this colour generation you were confident it was factor Xa activity, and not something else, because somebody had done a lot of research in developing this substrate?*

A. *Let me clarify. If the only protease there is factor Xa, then you can be confident, if this gets cleaved, that the activity is due to factor Xa. The substrates have some preference for different proteases, but it is not absolute, and so if you have a mixture of proteases, it is possible that one of the other proteases could cleave this substrate as well.*

Q. *Right. Usually, the only components that you are putting in, as I understand it, are just the substrate and factor Xa. Is anything else going into the test tube? Your sample of factor Xa in –*

A. *Sample salts, usually a carrier of some kind, et cetera, but the only enzyme typically that you put in there is factor Xa.*

Q. *I see. If we could have a look back in your first report, 6.42....Could you just explain that PT and aPTT assay to my Lord?*

A. *Yes, certainly. So there were a number of different types of clotting assays available, but I think it is fair to say that the two most commonly performed were the PT and the aPTT. The PT assay is short for prothrombin time. It is an assay that measures the activity of multiple clotting factors, and their ability to form a clot. So that assay is triggered by a reagent called a thromboplastin reagent. It contains relipidated tissue factor from some source. That is added, along with an excess of calcium ions, to citrated plasma. Citrate is a chelating agent for calcium, so if you overcome that chelation of calcium, then clotting is allowed to proceed. Many of the steps in clotting are calcium-dependent. So to conduct this assay you pre-warm plasma, you mix it with this thromboplastin reagent and calcium, with some kind of stirring, and you measure the time between the addition of that reagent and the formation of a clot, a plasma clot. This happens when fibrinogens convert into fibrin and it spontaneously polymerases to make a gel. Those clots are detected by different mechanisms, sometimes physical, sometimes optical, but there are various ways to determine when a clot happens. So the prothrombin time is the time between adding this reagent and the detection of the clot. They are typically set up to clot within about 13 seconds, something like that. The aPTT is short for activated partial – you know, what I just saw a mistake in my report. It says 'activated prothrombin time'. I am sorry, that should be 'activated partial thromboplastin time'. I did not detect that before this.*

Q. *Do not worry, I had not noticed it either.*

A. *It should be 'activated partial thromboplastin time (aPTT)'. I should back up, I am sorry. The prothrombin time samples factor VII, factor X prothrombin, and fibrinogen among all of the blood clotting proteins. Since there are other blood clotting proteins –*

Q. *Sorry, before you go on, is that the external or internal clotting pathway? What is the intrinsic or extrinsic –*

A. *So the prothrombin time, right, is the extrinsic clotting pathway, also called the tissue factor clotting pathway, and this assay is triggered by adding a relatively large amount of tissue factor.*

Q. *So it is mimicking a ruptured blood vessel or something like that; is that right?*

A. *To some extent, yes. In vivo, this pathway can also include factor IX and factor VIII, but the way the prothrombin time assay is set up, there is no contribution of those two clotting factors to the clot time.*

Q. *And this is....the chief reason why people also use the aPTT. It also samples – its clot time is also dependent on factor VIII and factor IX, which are the clotting factors that are missing in haemophilia A or haemophilia B respectively. The aPTT is conducted in a much different way. The initial stage is mixing the citrated plasma with basically an activated partial thromboplastin reagent, which is a very artificial activator. It typically is something like diatomaceous earth or ground-up clay or a chemical called ellagic acid. This activates the contact pathway of blood clotting, which goes through factor XII and plasma prekallikrein. Once you have a lot of XIIa, it activates factor XI to XIa. XIa then activates factor IX to IXa. IXa then assembles with its protein co-factor, factor VIIIa. The aPTT reagent has phospholipid vesicles in it to allow the VIII/IXa complex and all the downstream clotting cascade members to assemble on their (unclear). The VIII/IXa complex then activates factor X to Xa. At that point, the rest of the clotting cascade is the same as with the PT assay. So the advantage of the aPTT is it samples clotting factors that are known to be important and bleeding that are not sampled by the prothrombinase – excuse me, the PT assay, and that would include factors XI, VIII and IX, chiefly.*

Q. *I am grateful. I understand this is mimicking or modelling the intrinsic pathway, and it is the intrinsic pathway which is engaged. If you take a blood sample, put it in a test tube, and you get the blood clotting, that is the intrinsic pathway that is being implemented in those circumstances; is that correct?*

A. *Yes, that is correct. Glass, it turns out, is an activator of the intrinsic pathway.*

Q. *I am grateful. If I could ask you just to have a look at the cross-examination bundle. Do you have a bundle DXX? Go to tab 8. There should be a paper by Brigitte Kaiser, which is from 1998 'Drugs of the Future'. If you just have a look at page 427. It has a heading just at the bottom on the left-hand column 'Anticoagulant actions'. It says, 'The anticoagulant potency of protease inhibitors both in vitro and in vivo depends on the mechanism of enzyme inhibition, the affinity to the enzyme, and thus the inhibition constant, as well as on their stability in blood or an interaction with other blood constituents. To measure anticoagulant effects, global clotting assays such as thrombin time (TT), activated partial thromboplastin time (APTT) or prothrombin time (PT) can be used.' These are measurements of anticoagulant actions, if you put in a putative anticoagulant into the test, are they not?*

A. *They can be used to detect anticoagulants in these clotting assays, that is correct.*

Q. *And the difference between these assays, and the chromogenic assays, is the chromogenic assay is measuring binding to free factor Xa, where, on the other hand, these assays we have been discussing, the aPTT and the PT, are actually measuring, or measuring any inhibition of factor Xa in the prothrombinase complex?*

A. *I think that is largely true, although it is not entirely, even these days, clear if factor Xa that is initially generated is not important in converting factor VII to VIIa and the initial conversion of factor V to Va without being in the prothrombinase complex. In fact, there are recent studies that show that activation of factor V by free factor Xa might be more important than had been previously appreciated. But I*

think it is fair to say that in 2000 most of the attention would have been directed on the role of factor Xa and the prothrombinase complex in modulating clotting times in these kind of assays.

Q. *The chromogenic assay, although it gives you a measure of the ability to inhibit free factor Xa as against this substrate, it is not a direct measurement of reduced clotting time, and it may not even represent reduced clotting time because the kinetics are very different in the prothrombinase complex. That is correct, is it not?*

A. *Yes, the efficacy in the chromogenic assay and the efficacy in a clotting assay can be different, you are right.*

Q. *If we go to tab 7....[to] a paper by Taniuchi, a 1998 paper....Have a look at the first few lines in the summary. It is the discussion of YM-60828 which was found to potentially inhibit human factor Xa following oral administration. It shows high affinity for factor Xa at 1.3 nM activity. It did not affect thrombin, and doubled factor Xa clotting time, prothrombin time and activated partial thromboplastin time. We can see the sorts of assays that were performed to find out if this compound had an effect on coagulation, and we can see those on the next page, so that is page 266, if you have the red numbers, where they say, 'The hydrolysis rates' – I am just looking at the bottom left-hand column, 'Inhibitory Effects ... on Serine-proteases'. It says, 'The hydrolysis rates of synthetic substrates were assayed by continuously measured absorbance ... with a microplate reader', and that is the chromogenic assay, as I understand it. We can see at the top of the next column the compound they used, S-2238. That is the colour assay we were talking about; is that right, or broadly speaking something similar?*

A. *Yes, these are chromogenic assays.*

Q. *Then we have plasma clotting times in the next heading, and the plasma clotting times were performed using a coagulometer and they used PT and aPTT. We can see the results in Table 2, two-thirds of the way down that column, and they have a prothrombin time and an activated prothrombin time. Do you see those on Table 2, the bottom two entries?*

A. *Yes, I do.*

Q. *It is CT2 in micromolar, and they say if we go to the legend at the bottom, 'CT2 indicates concentration required to double clotting time.' So this is what the authors here are doing, and they are measuring the anti-clotting effect of YM-60828, using those assays; yes?*

A. *Yes, that is correct.*

Q. *They cannot get that information from the chromogenic assay, can they?*

A. *They are different, I agree.*

Q. *I think we can put that away. I just want to have a look at the application....If I could ask you to go to page 169....From line 22 there is a discussion of the chromogenic assay, using the substrate S-2222 which we have discussed. Then I just want to jump down to the bottom of 170, so antithrombotic effects. Do you have the last two lines? ...'The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model.' It is then described. As I understand it in a nutshell, the rabbit has the veins in its neck dissected out and the blood taken externally from the body is passed over a silk thread, and that will cause a thrombus to*

form, and then you can test your drug to see the extent to which coagulation is inhibited; is that correct?

A. *Yes, let me just clarify. You actually access both an artery and a vein, and you put a loop in, so that blood exits the artery, goes through the loop and comes back in through the vein, and enters the vein. So you have created a circulation loop so that there is no blood loss in the animal. But, yes and then you introduce something into that loop that will trigger the formation of a thrombus.*

Q. *That is the assay in the application, which is a direct measurement of the ability of compounds to coagulate or to inhibit coagulation, rather. They do not make any reference to the PT or aPTT assays which were commonly used in this document, do they?*

A. *I do not recall them mentioning PT and aPTT.*

Q. *However, using the assays in the patent, if you want to assess the ability of a compound to inhibit coagulation, this is the test you have to do, the rabbit arteriovenous test. You cannot get there just through doing the chromogenic assay?*

A. *Well, you would do the chromogenic assay to identify whether it inhibited the target that you want, and with what sort of affinity, and then you would want to follow that up, if you felt that the in vitro tests were promising enough. With in vivo efficacy, that is an important part of the whole process.*

Q. *You do not know, until you have done that, either in an aPTT assay, PT assay, or the venous shunt model, if the compound is going to have an impact on coagulation?*

A. *Well, it is very likely to have an impact on coagulation if it inhibits the enzymatic activity of factor Xa in vitro, but how effective it would be in vivo would require an in vivo test, I agree.*

Q. *Let us just have a look. I just want to go to....a paper you refer to in your report, if you recall, Zhu & Scarborough; yes?*

A. *Okay.*

Q. *If I could just get you to read where it says 'Proof of principle' so that is on the first page of the paper. If I can get you to read that first long paragraph....Tick anticoagulant peptide, that is a naturally-produced product from a tick, which when the tick feeds on an animal host it stops the blood coagulating so that the tick can feed, and the antistasin is the equivalent in the leech; is that correct?*

A. *Yes.*

Q. *We can see how active they are against free factor Xa. We have Kis of 0.18 nM, and 0.05 nM respectively, so they are highly specific for factor Xa and then it says it has a 50,000-fold selectivity over other related serine proteases. Then it has a second figure. If we drop down a little, it says, 'The affinity of r-TAP for FXa assembled in the prothrombinase complex (K, = 6 pM) is even greater than that for free FXa (K, = 180 pM). Both r-TAP and r-ATS are highly effective antithrombotic agents in several animal models of thrombosis.' Of course, it is that activity in the prothrombinase complex, the 6 pM activity, which is of importance to the tick, if I can put it that way, is it not?*

A. *Yes, the tick's food supply depends on the blood not clotting.*

Q. *But it is the level of inhibition in the prothrombinase complex which counts, as we have discussed, not the free factor Xa, because the free factor Xa is not really doing anything, is it?*

A. *Well, with the proviso that I said before, that especially recent research has suggested that free factor Xa plays perhaps a bigger role in the initiation of clotting than had previously been appreciated, because the initial conversion of factor V to Va is thought now to involve some action of Xa, so putting that aside, the ticks clearly developed an inhibitor that goes over the prothrombinase complex with high specificity and affinity.*

Q. *Then we see they tested it in AV shunt venous thrombosis model, which presumably is similar to the model we have just been discussing; yes?*

A. *Yes.*

Q. *Then if we go through this paper, we can see another example. So if we go to the next page, 79, and then look at the right-hand column, four lines down, they are discussing a particular compound. I do not think it matters too much what the details of the compound are, but it is a peptide mimetic, and they say expansion of the ring to produce 7, that is compound 7, increased the potency, and then they give IC50 figures for factor Xa, factor Xa in the prothrombinase complex and thrombin. So they are interested not only in its activity for free factor Xa, but also if it is going to work in the prothrombinase complex, which is why they have measured both; correct?*

A. *Yes, I think that is a fair statement.*

Q. *I can go through picking them out, but there is probably not a great amount of benefit, but let us look at one more. If we go to page 80, 80 on the left-hand column, compound 25 has values of 17, 50 and 20,000 nM for factor Xa, factor Xa in the prothrombinase complex and thrombin respectively. That is the data that is presented fairly systematically through this paper; do you agree?*

A. *Yes.*

Q. *Then if we look at one more perhaps on page 85, left-hand column, ZK-807834. It is not only highly potent for free factor Xa but also against factor Xa in the prothrombinase complex, and is remarkably selective. It has a Ki of 0.11. That is the free factor Xa. Then 6.6 in the prothrombinase complex. We can see some quite big differences. That is a 60-fold difference, is it, between the activity in free factor Xa and the activity in the prothrombinase complex; yes?*

A. *Yes.*

Q. *If we go to page 92 of this paper, we are now talking about non-amidino factor Xa inhibitors. Do you have the right-hand column, professor? They say: 'To achieve the desired oral bioavailability and half-life suitable for once-a-day dosing, Zeneca has exclusively focused on the design and discovery of selective and potent FXa inhibitors by using a pyridine ring as a P1 benzamidine mimic. These inhibitors are remarkably selective (they do not inhibit, thrombin, trypsin, t-PA, APC and plasmin)', I will discuss those with you later, 'and quitepotent (IC50 of less than 50 nM against free FXa). P1 – Pyridine based FXa inhibitors might have improved oral bioavailability and longer duration when compared with diamidino or mono-amidino compounds. However, it is not known if these inhibitors would be potent against FXa in the prothrombinase complex or have the desired in vivo efficacy in the animal thrombosis models.' What the authors are saying there is, look, we do not know how effective these compounds are going to be, because we have not tested them in the prothrombinase complex, or*

they have not been tested in the prothrombinase complex and they have not been tested in a thrombosis model such as the AV shunt. That is what the authors are saying there; yes?

A. *Yes, that is what they are saying.*

Q. *That would be the skilled person's understanding if a compound had not been tested in either a prothrombinase complex or in some sort of in vivo, a PT assay or an AV shunt. They would not know how effective the compounds are going to be, would they?*

A. *You are correct, they could have different potencies in those other assays compared to the chromogenic assay. You are quite right.*

Q. *Then if I can go back, sorry, still in the same paper, and just have a look at a compound, a very well-known compound. The Daiichi compound is just drawn on page 78 in the box on the top of the left-hand column where you can see the structure. You are in broad terms familiar with DX-9065a, professor?*

A. *Just in the broadest terms.*

Q. *If I can perhaps pick it up at 81, there is a discussion about compounds. They say: 'DX-9065a was the first newly diamidino FXa inhibitor to be highly selective and modestly potent.'....It has a Ki that is modestly potent, Ki of 41 nM and IC50 of 70 nM against free factor Xa, and does not inhibit thrombin. 'It is also quite selective for FXa versus trypsin, plasmin, and t-PA ...'. Then I taught we could read on to the next column, and drop halfway down: It says: 'The antithrombotic effects of DX-9065a were compared with r-TAP in rat silk thread anchored arteriovenous (AV) shunt thrombosis model.' Then it gives the inhibitory dose values of 0.6 and 0.0007 [sic] for r-TAP. So what they are doing there is they are now asking the question will this DX-9065a, whoever did this experiment was asking, be effective in inhibiting coagulation. That is what is being referred to there, is it not?*

A. *Yes, but for the record I would like to point out you added an extra nought.*

Q. *I am sorry.*

A. *It is 0.007.*

Q. *Okay, yes.*

A. *Correcting that, I agree with you.*

Q. *Then going on to the next paragraph on the next page, it is quite a long paragraph, just at the very end it says: 'In rabbits, DX-9065a (iv, sc or po) inhibited stasis-induced thrombosis after injection of tissue factor with ED50', and itgives the figures of 0.03, 0.3 and 50 mg/kg. So they are now actually testing this in a rabbit and they are observing that the oral administration is much less effective because thereis fairly poor bioavailability for this compound. That is the conclusion that the skilled person would draw from that; yes?*

A. *Yes.*

Q. *That would have been known to the skilled biologist, that there were issues with bioavailability for a number of these compounds, oral bioavailability?*

A. *Yes, it was an important property of any potential oral anticoagulant.*

Q. *Are you in a position to assist the court – we say it is fair that those working in 2001 were only really interested in compounds it which were orally bioavailable. It is just not practical for patients taking these medicines to continuously keep injecting themselves. You agree?*

A. *Well, I only partially agree with that. That was certainly a goal, to develop better oral anticoagulants that could replace warfarin and other vitamin K antagonists, but there were also activities at the time to try to come up with improved alternatives to heparin, which was an injectable anticoagulant at the time. There were development of, for example, thrombin inhibitors that were used injectably. So it was certainly a major goal to develop oral anticoagulants, but there is utility for injectable anticoagulants as well.*

Q. *Let us move on. We will come back to Zhu, but I just want to take a little diversion. Factor Xa is a member of the family of trypsin-like serine proteases; you are familiar with that, of course, yes?*

A. *Yes.*

Q. *And other members of the family arise in the coagulation cascade, including, I have a very short-list here, thrombin, plasmin, protein C, t-PA and urokinase. You agree those are all serine proteases; yes?*

A. *Yes.*

Q. *They are all trypsin-like serine proteases?*

A. *Yes, they are.*

Q. *Trypsin is also, of course, a trypsin-like serine protease. That is an enzyme that breaks down protein in the gut. It is a digestive enzyme, is it not?*

A. *That is its major role, yes.*

Q. *It sounds like there were other roles as well? Did you want to –*

A. *There are multiple trypsin genes, and there are reports of some of them being expressed in other tissues. There were also trypsin in those tissues that are much less clear. The best known role of trypsin is digestion of food in the small intestine.*

Q. *Because of the relationship between serine proteases, trypsin-like serine proteases, it was known that many factor Xa inhibitors, to a greater or lesser extent, inhibited other serine proteases, trypsin-like serine proteases, did they not?*

A. *Yes.*

Q. *And that needed to be tested for?*

A. *Yes.*

Q. *There are good reasons why factor Xa inhibitor should not interfere with the activity of trypsin, focusing on trypsin initially, because, of course, if it is given orally it is going to be coming in contact with trypsin in the gut; yes?*

A. *Yes, if we are talking about the use of these anticoagulants in terms of administration to patients, then selectivity against trypsin is important. If you are talking about using them as an anticoagulant in test tubes in which you draw blood, then inhibition of trypsin would be irrelevant. I agree with the goal of treating thromboembolic diseases selectivity against other serine proteases it is important.*

Q. *Indeed, we could go further than that and say it is crucial?*

A. *It is very important, I agree.*

Q. *I also wanted to pick up some of the other factors. Can I first ask you to go to C.1, tab 2? This is Dr. Leadley's report. I just want to pick it up because there is a helpful drawing here on page 71 in the red numbers.*

A. *Yes, I am there.*

Q. *We see here quite a complicated drawing. This is mostly for my Lord, but I am sure you are very familiar with this, Professor Morrissey, and see patents where we do not. Right in the middle we see factor X with an narrow to factor Xa. Then from factor Xa we see added in Va calcium, and that is the prothrombinase complex. Do I have that right?*

A. *Yes, Va calcium and phospholipid.*

Q. *Phospholipid, yes. We can see the conversion of prothrombin to thrombin, which is right in the middle at the bottom. Then if we follow it through to the right of the page, we can see thrombin. You have factor V and you can see aPC. You have aPC, which is, as I understand it, involved in returning factor Va back to factor V. So it is deactivating factor Va, which is part of the prothrombinase complex. Do I have that right?*

A. *Well, that is what the document shows. Of course, this is a very simplified version of the clotting cascade, and it does not really return factor Va back to factor V. It damages factor Va. It proteolytically damages factor Va. It is more accurate to call it factor Vai, which is inhibited factor Va, and that is an irreversible step.*

Q. *But it is reducing the amount of factor Va and therefore it is reducing clot formation?*

A. *Yes. Va and VIIIA are its two main targets.*

Q. *Thank you. I think we can probably leave that open because I am coming back to it. Then we can look....[at] the fourth edition of Haemostasis and Thrombosis....On page 19 you will see a diagrammatic illustration of fibrinolysis pathways. I have a feeling you are going to tell me this is a simplification.*

A. *Of course.*

Q. *Just looking right at the bottom, fibrin is a central part ofa blood clot, or a thromboembolic clot, and we can see fibrin there being changed to FDP, which is fibrinogen deposition products. This is fibrinolysis. This is a natural process acting against a clot which is breaking down the fibrin in the clot. Do I have that, broadly speaking, correct?*

A. *Broadly speaking, correct. I would have called them fibrin degradation products, but, yes, the concept is the same.*

Q. *We can see there are some important enzymes involved in potentiating this pathway. Just above the fibrin we see plasmin. That is a serine trypsin-like protease which is involved in this process; yes?*

A. *Yes.*

Q. *And we can see just to the right urokinase, which is another trypsin-like serine protease which is involved in this process; yes?*

A. *Yes.*

Q. *We can also see tPA on the left-hand side, sort of towards the bottom just above plasminogen, and that is another trypsin-like serine protease involved in this process of fibrinolysis; yes?*

A. *Yes.*

Q. *Thank you. You can put that away. I think we might still have Dr Leadley's report out, and if you go to ...paragraph 5.25....Titled 'Fibrinolysis'....[H]e says: 'Fibrinolysis is a normal process that prevents intravascular thrombi from growing and is essential for re-establishing normal blood flow. The process is mediated by plasmin, which is present in the circulation as an active precursor, plasminogen. Like the factors of the coagulation cascade, plasminogen is a zymogen*

which convert to the serine proteases, plasmin, once activated. Plasminogen activation takes place either by the action of tissue plasminogen activator (tPA) or urokinase.' We have seen that. That is what we have just been looking at; yes?

A. *Yes.*

Q. *If you want to reduce clotting, or a thromboembolic disorder, the last thing you want to do is inhibit the natural fibrinolytic process. You want to avoid doing that like the plague, do you not?*

A. *Avoid it like the plague, I am not sure, but it is not a good target to go after I agree. So you want selectivity of those proteases in the fibrinolytic system.*

Q. *If you go back to page 82, so back in Zhu & Scarborough....[i]n the bottom left-hand column, page 82, we were just looking at the rabbit data, if you recall. If you drop down, then there is then a reference to DX-9065a from Boehringer Mannheim. If we drop down to the next paragraph, there is a reference to Yamanouchi using DX-9065a. Then we can drop down to the very last word of that column, and it says....[t]hey are talking about the Yamanouchi program.'This program has produced YM-60828', and there is an alternative salt, 'as a development candidate. This compound is structurally very similar to DX-9065a but is much more potent against free FXa ... and FXa in the prothrombinase complex', and the figures are given, 'and is significantly easier to synthesise. YM-60828 does not significantly inhibit thrombin ... t-PA ... or plasmin.*" *The importance of tPA and plasmin, they are not just picked for academic interest, the importance is that they are fibrinolytic enzymes, are they not, and you do not want to inhibit them if you are trying to produce an anticoagulant; that is correct? That is why there is references to them; yes?*

A. *That is largely correct. You want the net effect of your anticoagulant to be indeed anticoagulant, and it is strongly inhibited in the fibrinolytic system it would not have a net anticoagulant effect.*

Q. *If we move on to page 92, we can see there is reference to another compound, so the right-hand column, first full paragraph: 'To achieve the desired oral bioavailability and half-life suitable for once-a-day dosing, Zeneca has exclusively focused on the design and discovery of selective and potent FXa inhibitors using a pyridine ring as a P1 benzamidine mimic. These inhibitors are remarkably selective (they do not inhibit thrombin, trypsin, t-PA, APC and plasmin)', and again the authors are there speaking about the fibrinolytic and the APC, which is the anti-clotting, if I can put it....That is why there is a reference to these enzymes here again, because they would be of concern if the product was inhibiting those fibrinolytic enzymes; yes?*

A. *Yes, if they were potent inhibitors of those enzymes that would be a problem.*

Q. *Then, finally, if we can go to page 77 and just look in the left-hand column, the first paragraph, and about halfway through it says....'A host of pharmaceutical companies has thus been actively pursuing FXa inhibitor programs with the goal of discovering potent and specific FXa inhibitors as replacements for warfarin. These inhibitors should: (a) be highly potent against FXa and FXa in the prothrombinase complex; (b) be highly specific to FXa versus thrombin, trypsin and other fibrinolytic enzymes such as tissue plasminogen activator, APC and*

plasmin', and then there is a reference to in vivo efficacy. Again we can see this paper emphasizing that it would be the view of the skilled person, would it not, in 2001, it was absolutely crucial that these compound, these putative clinical candidates, were not inhibiting the fibrinolytic enzymes or for that matter APC?

A. *Yes, they need to have much better ability to inhibit Xa than those other enzymes, I agree.*

Q. *We see reference to thrombin a couple of times, selectivity over thrombin, and I think you deal with that in your report at 6.36, so perhaps we can just have a quick look at that. Your first report....*
You set out there – I do not think we need to read them all...that by 2001 it was appreciated that factor Xa inhibitors had real advantages over thrombin inhibitors, and that is why people skilled in the art were looking for selectivity over thrombin; correct?

A. *Let me clarify. There was a lot of discussion in that timeframe, around 2000, about which would be the better target, thrombin and factor Xa, and there was a lively discussion among practitioners in the field at that time. There were some people who felt thrombin would be a better target, some people who thought Xa would be a better target, and each side marshalled their arguments. So these were the kind of arguments that were being made at the time.*

Q. *I am grateful. You can put that away for a minute, I think. If you could have a look at....Quan and Wexler. You see their address is DuPont....And Current Topics in Medicinal Chemistry 2001....I only want to look at it very briefly, just one passage. If you go to the first page in the introduction, the right-hand column, it says: 'For a fXa inhibitor to be an effective antithrombotic agent....it must demonstrate both adequate potency and selectivity. So 'must' is quite strong language being used here. 'From a selective point of view, the compound should not compromise the physiological or pharmacological fibrinolytic pathway by inhibiting enzymes such as t-PA or plasmin and should not inhibit activated protein C. Additionally, to be able to determine whether a 4-fXa inhibitor will have advantages in terms of efficacy or lower bleeding risk in preclinical and ultimately in clinical settings, selectivity for fXa over thrombin is necessary.' I understand your point that there may have been people who favoured thrombin and people who favoured factor Xa. I understand your evidence on that. It is absolutely clear that everybody understood, and the skilled person would have understood in 2001, the first point being made is that any potential candidate should not compromise the physiological fibrinolytic pathway or inhibit activated protein C. That would have been well understood, would it not?*

A. *Yes, with the clarification that the selectivity is never going to be absolute, but you want a substantial difference in activity against the target Xa versus these other enzymes.*

Q. *Let us have a look at another one....This is a paper by Rai, 2001, a medicinal chemistry paper....So 104, left-hand column: 'Trypsin-like....enzymes are involved in numerous physiological processes in the body. Specifically many of....the enzymes involved in thrombosis and fibrinolysis are trypsin-like. For a putative drug to have a favourable pharmacological profile, selectivity against anti-targets is critical. Several reasons for endeavouring to achieve thrombin selectivity has*

been outlined earlier. Plasmin mediates fibrinolysis, the process of blood clot to dissolution, and therefore a potential anticoagulants should be selective against plasmin. Selectivity against trypsin is important for favourable pharmacokinetics due to the high concentration of trypsin in the gut.' Again, we have another author here emphasising that it is important to show that you are selective against the potential anticoagulant components, including plasmin, and those involved in fibrinolysis. So this was very much in the thinking of the skilled person, again in 2001, was it not?

A. *Yes, I agree.*

Q *...If you are interested in a putative candidate for treating thromboembolic disorders, an acquired characteristic of that candidate must be that it is selective over fibrinolytic enzymes, and selective over trypsin.*

A. *Yes, those are important properties.*

Q. *They are not only important, they are necessary properties, are they not?*

A. *Yes. The degree to which they are selective can be debated, but it is important. It is very important that they are selective, I agree.*

Q. *Can we go to....Dr Leadley's report, 5.86....We have already seen quite a lot of these in Zhu & Scarborough, but what Dr Leadley did is he set out the sort of compound that people were working with in 2001. We see that they have activities against free factor Xa in the picomolar and low nanomolar ranges, so we have 0.1 nM, 7 nM, 22 nM. You do not disagree that that is the sort of typical activities that the skilled person was interested in in 2001; yes?*

A. *I agree.*

Q. *I would like to go to....a 1997 paper by Prasa....Then if I could ask you to go to the last page, this is the discussion, and go to the second last paragraph.... There is a reference to the prothrombinase complex in the fourth line, which you have described to us, and then it says: 'In clotting plasma factor Va is the limiting prothrombinase component, whereas FXa is present in large excess. Therefore, prothrombinase activity is not proportional to the amount of FXa present, so that FXa inactivation does not lead to a proportional decrease in prothrombinase activity.' As I understand it, what the authors are saying there is there is always lots of factor Xa around. If, for example, you knock out 5 or 10, 20% of the factor Xa, that may not make a difference. Is that essentially what they are saying in that passage?*

A. *That is what they are saying. I do not agree with their logic, frankly, but that is what they are saying.*

Q. *Obviously, we are interested in the skilled person in 2001. Would the skilled person in 2001 not agree with that, and, if not, could you explain why?*

A. *The assumption there is the factor Xa with the prothrombinase complex would have a different susceptibility to the inhibitor than free factor Xa. In fact, what was found was that these inhibitors, some type had similar Kis for the prothrombinase complex that they did for free Xa and sometimes very different. So it could vary. Their reasoning about the free Xa, I mean if the free Xa is not doing anything in clotting, or it plays a limited role in clotting, in that you have to inhibit the prothrombinase complex, then if you inhibit the Xa and prothrombinase*

complex by 20%, for example, you will reduce the rate of thrombin generation by 20%. So I am not following their logic. I would not have agreed with it in 2000 either.

Q. *They are making two different points, are they not? They are, first of all, saying that the factor Xa is present in a large excess. Do you disagree with that?*

A. *I am sort of agnostic on that, but it does not matter. If is the prothrombinase complex you are trying to inhibit, that that is what is important, this would – I do not understand. It is not enough of a large excess to soak up the inhibitor or something like that. I do not understand their logic there.*

Q. *Is not all that they are saying is that if you need – I do not know what the ratios are, but let us say for every factor Va molecule you need one factor Xa molecule, then the fact that the factor Xa is in shorter supply means it is the factor Xa which is determining the rate of the reaction. There will always be spare factor factor Xa for the factor Va may be in short supply. So if you knock out factor Xa, for every one factor Va molecule there will be another factor Xa molecule around to do the business?*

A. *Yes, but if it is not bound to Xa, it is not contributing to thrombin generation. It is not like once it gets inhibited it leaves Xa. It stays bound to Xa for a long time. I do not agree with this paragraph on multiple grounds. There are more than two possible explanations. I think they are kinetic arguments I do not agree with. I could take it apart for you if you want? There are many ways in which I do not agree with this paragraph. I think there are other potential explanations for their findings.*

Q. *I just want to concentrate on (a) at the moment. We are just discussing (a) at the moment, and this is the relative concentrations of factor Xa and factor Va. I think you said you are agnostic as to whether or not factor Xa is in excess and it may not make a difference?*

A. *It probably is in excess. They are probably right. The prothrombinase activity is not proportional – if that is true, then they are correct it is not proportional to the amount of Xa present. But what follows from that is that the inactivation does not lead in proportional decrease in prothrombinase activity. That would only be the case if the Xa in the prothrombinase complex had a very different Ki compared to the free Xa. Under certain circumstances, they could be correct.*

Q. *Let us read on: 'Moreover, the presence of high concentrations of its natural substrate prothrombin in the complex protects FXa from inactivation by an inhibitor.' What the authors are saying there is that within the prothrombinase complex, you are going to have lots of prothrombin and relatively little inhibitor. Do you dispute that?*

A. *Well, they are partly correct. So for protein inhibitors, that is largely the case. The protein inhibitors have a hard time inhibiting factor Xa in the prothrombinase complex in the presence of prothrombin. They are large and they do not haveaccess to the active site of Xa. Small molecule inhibitors do tend to still be able to inhibit factor Xa, even in the presence of prothrombin. And although there is a large excess of prothrombin, generally speaking the Km for most of these enzymes in the clotting system is very similar to the plasma concentration of the proteins. It is not that they are just dominated by substrate at all times.*

Q. *So the Km of what, do you say?*

A. *The Km for prothrombin utilisation by the prothrombinase complex. It is not that different from the prothrombin concentration in plasma. So it is not like the enzyme is 100% saturated at all times. In fact, you can see that small molecule inhibitors are still able to inhibit the prothrombinase complex. But they are right that protein inhibitors generally have a harder time inhibiting the prothrombinase complex in the presence of prothrombin.*

Q. *Let us read on. It says, 'On the other hand, the affinity of r-TAP to FXa is about 30 times higher when the enzyme is assembled in the prothrombinase complex compared to free FXa ...' So the tick has evolved actually to bind more tightly in the prothrombinase complex, as I understand, the tick TAP, if I can put it that way?*

A. *Yes, so it has evolved the ability to bind tightly to that complex, likely because it binds to both proteins, both Xa and Va.*

Q. *Then it says, 'Lower molecular weight inhibitors', which, of course, is what we are concerned with, 'are less potent in inhibiting complexed FXa during thrombin generation than one could assume from the Ki value determined for inhibition of free FXa.' So what the authors are saying there is, 'Look, you may have something that has a reasonable Ki in free factor Xa, but you cannot assume from that that it is going to be particularly good at inhibiting factor Xa in the complex'. That is what they are saying; yes?*

A. *Yes, there have been some small molecule inhibitors that have very similar Kis for free Xa and Xa in the prothrombinase complex, and other ones where there is quite a measurable difference in the Kis for the two.*

Q. *We are talking about 2001, professor –*

A. *Yes.*

Q. *– just to confirm. You are not disagreeing, as I understand it, with anything from the start of (b) to where we have got to so far?*

A. *No, I accept that it is not always the case that there is a big difference in the Ki between free Xa and prothrombinase complex, but there can be.*

Q. *Then they continue, 'Therefore, an inhibitor should have a high affinity to FXa (Ki value for inhibition of free FXa in the nanomolar range) to efficiently interfere in coagulation at the point of convergence of the extrinsic and intrinsic pathways.' As I understand, it you do not dispute that factor Xa inhibitors should have nanomolar activity, you do not dispute that?*

A. *You know, that is the most desirable affinity, but I should point out that, in the case of treating thromboembolic disorders, for example, you only want to partially inhibit factor Xa under any circumstances. If you were to completely inhibit Xa, the patient would bleed to death. So you have to dose your drug with whatever affinity it has, at a dose that will only partially inhibit Xa, so that you slow down the rate of thrombin generation. On the other hand, if you are using this drug, for example in extracorporeal circulation, then you really want to completely block thrombin generation for the duration of the procedure. So it is a bit more complicated than, I think, what you just said.*

...

Q. *...If we go to your expert report....[y]ou said, 'Nanomolar potency is the level of potency that the skilled team would generally be looking for when testing potential inhibitors.' I mean, that is for clinical use, presumably; yes?*

A. *Yes, I agree.*

Q. *...Going back to the paper we were on....[t]he authors are saying here, 'Therefore, an inhibitor should have a high affinity to FXa' – do you remember looking at that at the end of the passage? ... (Ki value for inhibition of free FXa in the nanomolar range) ...' The authors are not just saying that is nice to have, they are giving a scientific rationale as to why that is necessary. That is what they are doing, is it not?*

A. *They are. I mean, it is much preferable to have high affinity drugs, I agree.*

Q. *You have said you had some criticisms, I think, of the early stages of the reasoning of this, but you were not in the field at the time, presumably you were not addressing your mind to the specific issue as to what level of activity was required for the clinical use in 2001?*

A. *Well, you are right that I was not working specifically on that, but it is generally the case, I would agree, that lower Kis are quite a bit preferable to higher Kis.*

Q. *The authors here are not just saying they are better, they are saying they are necessary, are they not?*

A. *They are.*

Q. *You have not pointed to any contemporaneous documents which suggest otherwise, and by 'contemporaneous' I mean contemporaneous to September 2001 or before September 2001, which suggest otherwise?*

A. *That is correct.*

Q. *If we can have a look in your cross-examination bundle [the Stürzebecher paper]....I just want to see what they were doing here. So they refer to some materials and methods on page 246, and they were using the assay we are familiar with, the chromogenic assay, and they refer to that under the materials and methods, and they were also using an aPTT assay; is that your understanding?*

A. *Yes.*

Q. *They describe some results on page 247?*

A. *Right.*

Q. *And they start off referring to the inhibitory activity of new benzamidine derivatives. Sorry, I will just ask you to keep in mind the date. We are way back in 1989 at this point.*

A. *Right.*

Q. *And they say, 'Like ordinary benzamidines, in this type of inhibitor the 3-amidino derivatives were more potent inhibitors of F Xa than the isosteric 4-derivatives. Most of the compounds inhibited F Xa with Ki values in the 10 µm/1 range.' Yes?*

A. *Yes.*

Q. *Then they set out some data below, and we can see they have a little mini Markush there, and we can see in Table 1 the different substitutions, and then we have the factor Xa inhibition in micromols, and we see sort of 15, 10, 73, 120, There is one that is quite a bit better*

at 0.36, and then they have the aPTT coagulation inhibition assay data there as well; yes?

A. *Yes.*

Q. *Then, just taking it right from the very bottom of the text, under 'Results', they say, 'The structural variation caused a drastic reduction in the antithrombin activity. Changing of R2 to OH or an ester group increased the anti-F Xa activity and decreased the antithrombin activity ... The results obtained prompted us to design derivatives with other ester components ...' Then we can see the factor Xa activity is much better. We have 0.84 down to I think 0.29 maybe. There is 1.33 but then down to 0.24 is probably the lowest. The authors were not satisfied with the 10 µm activity, and they were trying to improve things, and they are now obtaining high nanomolar activity; yes?*

A. *Yes.*

Q. *We can see they go on and try other things, and in Table 5 they are doing a little better even so. What I wanted to go to, really, was the discussion. If you look at the second paragraph, they say 'The inhibitor studies' – do you have that, professor? ...So they talk about the inhibitor studies were carried out with bovine factor Xa. 'Moreover, for several compounds Ki values were calculated using human F Xa.' They say there were only slight differences. Then they continue, 'Furthermore, we have assessed the anticoagulant activity of the 43 compounds presented here, which varied from one another in their inhibitory effect on F Xa and thrombin. Surprisingly, the antithrombin activity much more than the anti-F Xa activity of a compound contributed to the anticoagulant effect. In order to demonstrate the correlation between the inhibitory activity of the compounds and their anticoagulant potency, a regression analysis was carried out as reported in part previously [15]. The linear regression analysis showed that there was no correlation between the Ki values for inhibition of F Xa and the effective concentrations for prolongation of aPTT ...' So what they are saying here is within the context of this study, and the factor Xa inhibition they were getting, that was not having an effect on coagulation, it was the inhibition of thrombin that was having an effect on coagulation. That is what they are saying, is it not?*

A. *For the aPTT clotting assay?*

Q. *Yes.*

A. *Yes.*

Q. *So at these levels, the authors are reporting that there is evidence that actually inhibiting factor Xa 10 µm, or high nanomolar, was having no effect on coagulation properties. That is what they are saying, is it not?*

A. *Yes, there are multiple potential explanations for the results, but that is what they are saying, I agree.*

Q. *Let us read on. I am going to the last two paragraphs of the discussion, over on the next page. After three lines, it says, 'What is the reason for this finding, which is contradictory to the concept of TIDWELL et al. [7]? The fact that inhibitors of thrombin much more effectively interfere in the coagulation process than do inhibitors of F Xa obviously results from the different mode of action of the two enzymes. Thrombin cleaves its substrate fibrinogen in the fluid phase of plasma and an inhibitor is able to interfere with this reaction. In contrast, the F Xa-*

catalysed activation of prothrombin occurs in a complex consisting of phospholipid' – so that is the prothrombinase complex; yes?

A. *Yes.*

Q. *– 'factors Va and Xa and prothrombin, the so-called prothrombinase complex. During complex formation not only the enzyme F Xa but also the substrate prothrombin accumulatein the interface shell. The concentration of prothrombin in plasma amounts to about 1 µmol/l; however, upon complex formation it increases by 1000 times [l6]. Obviously, at such high concentration the substrate protects F Xa from being occupied by the inhibitor. Therefore, an effective inhibitor must possess an extremely high affinity for F Xa, otherwise it must be present in plasma in very high concentrations.' So, again, I mean this is making the point not just that it is nice to have something more active, but they are saying that if you have these high micromolar, 10 µm or high nanomolar activities, they are just not going to have an effect on coagulation; that is what they are saying?*

A. *That is what they are saying. I disagree with their conclusion. I would be happy to explain why.*

Q. *We will come on to that. First of all, you did not have a contrary view in 2001, did you, because you were not in this field?*

A. *I was in the field of understanding how the initiation steps of coagulation happened at the biochemical level.*

Q. *But you had not formed a view that you could get anticoagulant activity with micromolar Kis, had you? You had not formed that view in 2001.*

A. *I was not thinking about what sort of dosing of a Xa inhibitor it would take to give – to work in vivo. That is a fair statement.*

Q. *So you have a view today, looking at this, that their reasoning may be unsound. Do you want to explain that to me?*

A. *Yes, well there are multiple reasons why the clotting assay that they are using might not work. In fact, oral Xa inhibitors, the field has found that you cannot accurately quantify the concentration or the effective concentration in a patient using conventional clotting cascades, neither the PT nor the aPTT are very sensitive to the circulating concentrations of factor Xa. In fact, people have developed special Xa-triggered clotting assays to try to identify or quantify the effective concentrations of these oral anticoagulant that target Xa. So the fact that they cannot get the aPTT to be very prolonged by a factor Xa is consistent with the experience in the field that factor Xa inhibitors by and large do not really change the clotting time of aPTT by that much. The PT and aPTT are set up to measure something completely different than Xa inhibitors. They have an overwhelming dose of activator of the clotting cascade in both cases. In large part because the people running the assays want to get a lot of assays done in a short period of time, so they want the shortest possible clot time. They are there to measure other things, like heparin or warfarin therapy, and that sort of thing. So they were optimised for those purposes, not to be sensitive to inhibition by Xa. So there are reasons why the aPTT was relatively resistant to adding Xa inhibitors. I do not agree with the conclusions that they are coming to, necessarily.*

Q. *That is using your knowledge from today. You are not suggesting that that was part of the common general knowledge in 2001, are you?*

A. *No, when the factor Xa inhibitors were first coming on, there was a lot of discussion about whether it would be necessary to monitor them. So warfarin therapy and other vitamin K antagonists are routinely monitored. The patients who were on those drugs have to come in and get a blood test, a PT, and the dose of their drug is adjusted based on the results of that PT. The hope was that you would not have to monitor patients who were on oral inhibitors of factor Xa, and in fact that is what has turned out. There was a lot of discussion about what if you did have to monitor, or what if you thought you had a patient who was overdosed, what assays would you use, so there was a lot of discussion at that time about how to measure this, how you would go about doing it, what assays to use and what have you.*

Q. *Let us just have a look at....another paper from 1999. Do you know this group, the Walenga group?*

A. *No, not particularly.*

Q. *If we look on the right-hand column. It says, 'The initial development' – do you have that – 'of factor Xa inhibitors, some years ago, was met with less interest than the development of thrombin inhibitors. These early inhibitors had low affinity to factor Xa, low selectivity and low potency [3,4]. Because of the increase in enzymatic activity of the coagulation cascade once the prothrombinase complex is formed, a potent factor Xa inhibitor is required with extremely high affinity for the enzyme. The first factor Xa inhibitors did not fulfil this requirement.' So they are saying that is required, they are not saying it is nice to have, they say it is required. They give a citation there, a reference [3], and if you have a look at reference [3], that is the Stürzebecher paper, is it not, that we have just been looking at?*

A. Okay.

Q. *What I am putting to you, professor, is that this was the view, in 2001, to those working in the art of trying to find new factor Xa inhibitors, was that it was required to have nanomolar activity, extremely high affinity, for the reasons given in the Stürzebecher paper and Prasa. There was a belief that it would not work if you had micromolar activity, not that it is better to have nanomolar, but it would not have worked with micromolar?*

A. *That is clearly the opinion of these authors, I agree.*

Q. *Just have a look at one more. You have made some criticisms of the PT and aPTT assays in the last answer you gave to me. You are not disputing that they were widely used. We have seen them in Zhu & Scarborough, to which you refer to, I think. They are in a lot of the papers. I do not have to go through them all. You are not disputing that they were being used in the industry to measure the ability to impact coagulation?*

A. *Oh, they were.*

Q. *(Pause) I am grateful to my learned friend. Just so my question is clear, they were being used to measure the effectiveness of factor Xa inhibitors?*

A. *They were often used to screen factor Xa inhibitors, that is true.*

Q. *Let me just have a look at this reference. I may not need to go to it. We will have a look at one more, perhaps the lastone. This is the Kaiser review....If we go to page 426, right-hand column.... 'Due to the dramatic increase of the catalytic activity of factor Xa after assembly*

in the prothrombinase complex an effective factor Xa inhibitor is required to have an extremely high affinity for the enzyme. Synthetic, directly acting factor Xa inhibitors developed and studied in the past had less selectivity over thrombin and, furthermore, the potency of these agents was modest, so that no final conclusions on the anticoagulant/antithrombotic potential of the inhibition of factor Xa could be drawn ...' Again, there was a belief in the art at the time in 2001 that this was necessary to have this extremely high affinity for the factor Xa enzyme, was there not?

A. *I think that was a common belief, yes.*

Q. *I think they have cited Stürzebecher as well, reference (31). Can we then turn to the application....I would like to pick it up at page 6...so from page 6, from line 6, through to the end of the page, there is a reference to certain pharmacokinetic properties, and I think you accept that the skilled biochemist would understand that these are characteristics that the skilled team would need to pay attention to; yes? ....[I]f you remember this passage, it describes a certain set of pharmacokinetic factors.*

A. *Right.*

Q. *I think you accept that these are characteristics that the skilled biologist would pay attention to; yes?*

A. *Yes.*

Q. *Let us have a look at them independently. It says, '... efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents ...' It talks about discovering new ones. Then it says, 'It is also desirable' – this is line 15 – 'and preferable to find compounds with advantageous and improved characteristics in one or more of the following categories, but are not limited to', and, first, it is pharmaceutical properties, e.g. solubility and permeability, and I think we have agreed that the skilled biologist would know about these things dissolve and they have to be absorbed, so it is not telling you anything new there, is it?*

A. *No, I agree.*

Q. *Then dosage requirements, lower dosages and/or once-daily dosing. Again, nothing really interesting in that, is there? Clearly dosing is required, once-daily dosing is preferable; you agree?*

A. *Yes, once-daily dosing is preferable, but more frequent dosing could happen. But, as goals, those are good goals.*

Q. *Then factors which decrease, this is (c), blood concentration peak-to-trough characteristics, and the skilled biologist would be familiar with the idea that the blood concentration goes up and down, depending on the dosing, depending on the half-life, depending on clearance, and it is desirable to have it going up and down as little as possible. That is just standard stuff, is it not?*

A. *Yes, it is, I agree.*

Q. *Then factors that increase the concentration of the active drug at the receptor, and there is no receptor in this case, is there? That seems to be a mistake. Do you agree?*

A. *In this case Xa is essentially the receptor for the drug.*

Q. *Receptors are quite specific things, are they not? As a biochemist, you must appreciate that factor Xa is not a receptor.*

A. *Except in the sense that often people do binding studies, evenwith enzymes, they will talk about receptor ligand interaction, but I agree, it is not a conventional receptor in the usual sense.*

Q. *You know, concepts of protein binding and volume of distribution, again this is all just very standard stuff, is it not?*

A. *Yes.*

Q. *Then, if we read down to the end of the page, it talks about drug-drug interactions, manufacturing costs. Again this is a list of desirable characteristics of pretty much any pharmaceutical you could imagine, would you not agree? It is a nice-to-have list.*

A. *I agree.*

Q. *There is no indication in the patent that any of these parameters: solubility levels, dosage requirements, clearance, have been measured and there is no data in respect of any of these parameters, is there?*

A. *I believe you are correct.*

Q. *Can we have a look on page 7. There is then a description of the summary of the invention. At line 33 on page 7, there is a reference to 'other objects', but apart from the reference to other objects, which I will come on to, this is all about contemplating factor Xa inhibitors as a therapeutic. I assume you would not disagree with that....*

A. *Well, the first paragraph mentions Xa inhibitors, and then it talks about various properties of the invention, the rest of that page.*

Q. *Sorry, I do not think there is much debate. It is clearly directed to pharmaceutical use, this page? We will look elsewhere, but this particular page.*

A. *I agree the page is directed at therapy.*

Q. *If you go to 168, using the black numbers, that is the section which starts 'UTILITY'....And take it from me, over to line 19 again there is just a reference to clinical uses....Then there is a reference to the anticoagulant at 19, 'The anticoagulant effect of compounds of the present invention is believed to be due to the inhibition of factor Xa or thrombin.' ....It is here teaching, 'The anticoagulant effect of the compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.' Yes?*

A. *That is what it says, yes.*

Q. *And this sort of suggests that the question of whether the anticoagulant effects are because of factor Xa or thrombin has not been investigated, and indeed there is no data in the patent which indicates the inventors have tried to distinguish factor Xa inhibition from thrombin inhibition?*

A. *Well, you are correct that there are no data on efficacy in the patent, other than a statement, a broad statement, that some of the compounds do inhibit factor Xa.*

Q. *Then we have looked at this section, I think we have the chromogenic assay, and then we have passages we may come back to, but it says, just at the end of 170, line 28, 'Using the methodology described above, a number of compounds of the present invention were found to exhibit Ki's of < 10 µm, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.' We cannot tell from this document which compounds were tested, if any, can we?*

A. *Well, there is a statement that they did find that some of them, at least a number of them, inhibit, so one has to assume that that is a true statement, but it does not disclose which ones, or how much inhibition.*

Q. *Then if we turn over the page, look at 171, line 18. It says, 'The compounds of the present invention may also be useful as inhibitors' – do you have that, professor?*

A. *Yes.*

Q. *– 'of serine proteases', and then it lists them out. So this indicates either that the compounds in the invention are not selective, or that selectivity has not been determined, as we have discussed; yes?*

A. *When I read that sentence, my understanding of it was that they disclosed a lot of compounds. Among the compounds, some of them may also be inhibitors of these other enzymes, and because of that they might be useful and then they list blood coagulation information, these enzymes play roles, you know, in different things in the body. So I did not read it to say that one compound was inhibiting all of those proteases at the same time.*

Q. *From the technical perspective, obviously my Lord can read it, but from the technical perspective certainly it could mean that a particular compound inhibits one or more of those, could it not?*

A. *Yes, it does not clarify that.*

Q. *Then, just dropping down, 'Specifically...the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.' We know anticoagulants, of course, are widely used. When you get a blood sample taken, as you have explained, the glass can set off a coagulation, I think was it in the intrinsic cascade of coagulation. When you have your blood taken usually, you have an anticoagulate in the blood tube which stops it clotting. That is correct, is it not?*

A. *Yes, that is often the case, unless the goal is to make serum, but you are right, if you need to process blood often there will be an anticoagulate in the tube that you collect the blood into.*

Q. *If you wanted to know whether a product was suitable as an anticoagulant, you would use a PT or an aPTT assay to assess that, would you not?*

A. *Those would be reasonable assays to use, yes.*

Q. *And I think you said to me earlier that even more than therapy, of course, slowing clotting is not going to be good enough for an anticoagulant, you have to stop it altogether; yes?*

A. *For this purpose, to keep blood fluid in a blood collection tube, yes, you need quite a high level of anticoagulation.*

Q. *And, again you need a compound that is extremely active in the prothrombin complex; yes?*

A. *Either that or you need to dose it at a very high level.*

Q. *Of course, in order to know if any factor Xa inhibitor is suitable, or has any prospect of being used as an anticoagulant, it is necessary to test it in a coagulation assay such as the aPTT or PT assay, is it not?*

A. *Yes.*

Q. *So the suggestion that any compounds of the invention could be used for this purpose, particularly with those low micromolar activities, is entirely speculative, is it not?*

A. *Well, they are predicting that, you know, that one of their inhibitors could be used for this purpose, you are right, but it is a prediction.*

Q. *It is a speculation?*

A. *Well, speculation, if you like.*

Q. *Then perhaps if you would just read on, 'Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit cleavage of small molecule ...' Again, I appreciate you may say there is an ambiguity in there, but it seems to be contemplating inhibition of thrombin, in addition to inhibition of factor Xa, so that is not really consistent with a class of selective compounds, is it, factor Xa selective compounds?*

A. *Well, it is unclear to me. It could mean that there are among the collection of compounds some specific thrombin inhibitors. It could also mean that an inhibitor might inhibit both Xa and thrombin. It is not stated very explicitly.*

Q. *If you had an inhibitor which was promiscuous enough to show significant activity against thrombin, in addition to factor Xa, then you would be particularly concerned it may be hitting other serine proteases as well?*

A. *Well, you would want to test that. Whether it cross-reacted to thrombin or not, you would want to test that.*

Q. *Then if you go to page 179. I think that is the next bit we need to look at. It says, 'The compounds of the present invention are also useful as standard-or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa.' ....By a standard or reference compound, what it is meaning is you could use one of these inhibitors to benchmark against other inhibitors. That is what it is talking about, is it not?*

A. *Right, for use as a positive control in studies.*

Q. *It does not matter what its activity is, if it is 1 µm, 10 µm, 100 µm, 1,000 mM, it could be used as a standard for that level of activity; yes?*

A. *I do not know about 1,000 mM.*

Q. *Okay, maybe I took it a little too far.*

A. *Within the 10 µm or lower, certainly.*

Q. *If it is negative, of course, it could be used as a negative control, could it not?*

A. *Well, that is true too.*

Q. *There is not really a factor Xa inhibitor in the universe that can be used as a standard, is there?*

A. *So Xa inhibitors encompass a large number of things, including protein inhibitors, whose mechanism of action is rather different. It includes slow binding inhibitors as well as fast-binding inhibitors. So if you were trying to use it as a control in a study, where you were looking at small molecule inhibitors, for example, that bound quickly, you would want to compare it like to like. So, I do not think the entire universe of Xa inhibitors would suffice.*

Q. *Any of the inhibitors in '131 – you know what I mean by '131?*

A. *I do.*

Q. *I mean, any of those could be used as standards; yes?*

A. *I suppose you are right, yes, unless you were trying to, you know, as I say, do a like-to-like comparison, or if you needed to have a special class of inhibitor in there, but yes, generally speaking, you are right.*

Q. *Before you used it as a standard in an assay, you would need to know precisely what its activity is; yes?*

A. *Yes.*

Q. *And you would need to know what its selectivity is; yes?*

A. *That would depend on the assay that you were doing, but for some assays, yes, I agree.*

Q. *So let us move on from that. It then goes on and says, 'The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions ...' That is the – you could use it as a component in the chromogenic assay. We discussed earlier, ordinarily you do not have any additional ingredients for your chromogenic assay, you just have your substrate, and your factor Xa sample, and you see is there factor Xa activity. That is what you normally do, is it not?*

A. *That is the most common use, but these chromogenic substrates are used in, for example, thrombin generation assays, in plasma, and so in those assays you trigger the clotting cascade and you put in a chromogenic or fluorogenic typically assay for thrombin, and then in real time monitor the cleavage of that assay in this complicated mixture of things that are going on. So, in those kind of complicated mixtures, I can imagine using a specific Xa inhibitor to prove that, or provide evidence that the cleavage of the S2222 was Xa and not another enzyme. None of these chromogenic substrates are very – they have some specificity for various proteases, but it is not absolute. For example, if you saw S2222 being hydrolysed, how do you know it is not thrombin that is cleaving it, especially since vast quantities of thrombin are generated during a clotting assay. You could try adding a specific Xa inhibitor and seeing if that activity went away, for example. That sort of utility, I think, is what they are getting at here.*

Q. *That is not what they are saying. You are hypothesising, reading between the lines, that that might be what they mean; yes?*

A. *I think that was my understanding here, that the Xa in an unknown sample, by adding a chromogenic substrate, and then if what they are saying is if you see PNA and test solutions compound, then one could conclude it was factor Xa that was present. Essentially, Xa was cleaving S22 and not some other unknown enzyme.*

Q. *You did not refer to this in your expert reports, I noticed. Is this something you have any familiarity with? Is it something you had done before 2001, or is this, again, sort of speculative?*

A. *Before 2001? Let me think about that. It is the kind of thing we might have done if we were trying to look at complex mixtures. I do not recall doing it myself.*

Q. *Again, the same question. That would apply to any factor Xa inhibitor, and including those in the prior art, the '131 prior art. I think you know what I am referring to.*

A. *I do.*

Q. *It would include any of those. They could be used equally well; yes?*

A. *Yes, in this particular application you would want to be certain that the Xa inhibitor was quite specific for Xa.*

Q. *Yes, you would. You would need to know that it was highly active and highly specific to be useful in an assay like this, would you not?*

A. *At least against the other enzymes that are likely to be present in whatever mixture you are trying to analyse.*

Q. *Again, until you have a factor Xa inhibitor that has demonstrated that activity and specificity, until you have that, this utility is entirely speculative, is it not?*

A. *Speculative, predictive.*

Q. *...Can I then go to your report....6.2....You very fairly said you were not in this field, and you have tried to identify the common general knowledge by looking at various papers. You refer to two textbooks here. Then...if we go to 4.4....you refer to some papers you were provided with, so the Leadley article...a paper by Turpie and Zhu & Scarborough, which we have been looking at. You consider serine protease inhibitors from 6.33. This is in your common general knowledge section....You start discussing these and you mention again Zhu & Scarborough. You mention at 6.38 the Robert Leadley article. Then at 6.40 you refer to an article by Spencer and Becker, you do not refer to anything else, unless I have missed one. I do not think so. Are those the only papers you looked at when trying to determine what the common general knowledge was, or did you look at many other papers and how did you decide which papers to look at?*

A. *I looked at some other papers, doing PubMed searches for what was available at the time. I did not look at a huge number of them, no.*

Q. *Which papers were they? Was there any reason why you did not let us know which papers you had looked at?*

A. *I do not recall exactly.*

Q. *But you found them yourself?*

A. *I found several myself.*

Q. *Okay.*

A. *Hogan Lovells suggested a few as well.*

Q. *Let us have a look. Let us move on to 8.2. Under plausibility. You say: "I have been asked to consider the question of plausibility. As part of my instructions in this case, I have been told that the legal standard in relation to a claim to compounds for a therapeutic use requires that the use of the claimed compounds for the claimed therapy would have been plausible to the skilled team. I have been instructed that the issue is whether the application discloses some reason for supposing that the assertion of efficacy is true. There must be reasonable scientific grounds for the skilled person to expect that the compounds might well work to treat the claimed indications.' The claimed indications you had in mind there was the treatment of thromboembolic disorders; is that correct?*

A. *Yes.*

Q. *Then you answer this question at 8.3. You say: 'If a compound had been identified by the medicinal chemist as being an effective factor Xa inhibitor with drug-like properties ...then, for the reasons that I discuss in the CGK section above and summarised below, the biochemist would anticipate that the compound would be a good candidate for a drug to treat thromboembolic disorders.' As I understand it, you have already been told that this is an effective factor Xa inhibitor; that is correct?*

A. *In this assumption, yes.*

Q. *Then in (a), (b) and (c) what you are effectively saying, if you just remind yourself of those. I would summarise it as saying that you are*

saying a factor Xa inhibition is a legitimate target if you are interested in treating thromboembolic disorders. That is essentially what you are saying. You are not saying any more than that, are you?

A. *That is what I am saying. There are precedents for expecting Xa to be an interesting target.*

Q. *That is contingent on having an effective factor Xa inhibitor in the first place?*

A. *Yes.*

Q. *Plainly.*

A. *Yes.*

Q. *If you can just have a look at what Dr. Leadley says....He said: 'The skilled pharmacologist in 2001 would not expect that a compound with a Ki in the low micromolar range i.e. between 1-10 µM to be useful as an anticoagulant for treatment or prevention of thromboembolic disorders. Compounds of interest to take forward for assessment in animal models and potential clinical development would by 2001, as a starting point have required low nanomolar in vitro potency against factor Xa.' Then I want to see how you responded to that, so that is in your reply report, which is at tab 5, I think, going back to D.1.*

A. *Mmm-hmm.*

Q. *You say at 3.2....'Dr. Leadley repeatedly refers to a lack of data in the WO652 application, including', and you list some paragraphs. At paragraph 6.50, Dr. Leadley states: 'if the potency, selectivity, and anticoagulant activity of Example 18 had been provided in WO652 it would have been of great interest to the skilled pharmacologist in 2001'. I agree with that.'' Then you refer to a 2007 paper by Pinto, so after the priority date, which publishes some data for apixaban. My understanding is you have not taken issue with anything that Dr Leadley has said in 6.23 in your reply report, have*

A. *Yes, I know what you mean. The only thing that I think that is a point of potential dispute is what would be the threshold to consider, something worthy of pursuing in terms of Ki values, but lower is always more preferable, I agree.*

Q. *We have been through that. It is not just a question of more preferable. It is a question of whether it will work at all, is it not? You have not managed to point to any papers, and I do not know if you found any in your reviews, which indicate that anyone in the art, who was working in this art in 2001, would have considered a 1-10 µm inhibitor as a credible candidate for clinical use?*

A. *They were credible lead compounds, but you are right, people were looking for higher affinity compounds than that.*

Q. *The thing about lead compounds in a discovery process is you may have a lead compound but then what you are doing to that lead compound is you are changing it to try and get better activity, are you not?*

A. *Yes.*

Q. *So, to be an effective factor Xa inhibitor not only do you need nanomolar activity, but you also need to show that you have specificity and that you are not going to be inhibiting to a significant degree the fibrinolytic pathways that we have discussed. That is correct, is it not?*

A. *Yes, you do need specificity. Exactly how high a Ki you could have and still go forward with a drug is not so clear, but the lower the Ki, the better, I agree.*

Q. *I will be submitting to my Lord that there is nothing in the patent specifications to suggest that apixaban, or any of the other exemplified compounds, and apixaban is Example 8, are effective and selective factor Xa inhibitors and have the potential to treat thromboembolic disorders. You cannot*
disagree with that, can you?

A. *There are no data on selectivity. There is only a broad statement about effectiveness, and it just gives an upper limit there. So I agree there are no specific data in the specification that address that.*

Q. *We have seen from the papers, when characterising a factor Xa inhibitor, and I am thinking particularly of Zhu & Scarborough that we have been looking at, it was customary in the art to specify a Ki against factor Xa and its selectivity. We now know that apixaban has a Ki against factor Xa of 80 picomolar, that is 0.08 nM, and that information, that apixaban had that activity, would be of considerable interest to the skilled reader of this application, had it been included, would it not?*

A. *Well, can I break your question up? You started, I think, by saying it was customary or something to put these data in, but you are talking about published papers there, rather than patents, I think.*

Q. *Yes.*

A. *Then you went on to ask about whether knowing that apixaban had such a high affinity for factor Xa would be interesting to the person with normal skill in the art or something, and I completely agree with that assertion.*

Q. *That information, and particularly if it was accompanied with selectivity data, is much more useful to the skilled person than the suggestion that apixaban might have an activity of less than 10 µm. It is information of a different character, is it not?*

A. *I agree it would be much more interesting.*

Q. *There were no conventions, and I am not talking about patent*
conventions, I mean scientific conventions or technical reasons, why that information would not be included in the patent specification, as far as you are aware?

A. *I cannot speculate on why they chose to not include data in the patent specification.*

Q. *Finally, professor, can I just ask you to go to '131. I think you have that somewhere.*

A. *You asked me to look at a few pages of '131, I believe; is that correct?*

Q. *I want you to go to page 264. You have looked at this previously, I think, yes? It is referred to in your report.....Now, I am not asking you to necessarily do a word by word comparison, but in terms of the potential uses for the drugs in '131, or the factor Xa inhibitors – sorry, first of all, pick it up at 264 where there is a reference to the rabbit model and there is a reference to Kis. As you know, it is very similar to the application we have been looking at and the patent in suit, but I want to go to 267 where there is a reference to potential uses, starting at 267, line 16, use of compounds as a standard....There is a reference to use of these products as standards and use of diagnostic assays. That is from line 16 through to line 32....Broadly speaking, these are the same potential in vitro applications....Sorry, there is something I meant to ask you earlier and I forgot. Just looking at 180....it says:*

'Compound of the present invention may further be useful as diagnostic agents and adjuncts. For example, the present compounds may be useful in maintaining whole and fractionated blood in the fluid phase such as required for analytical and biological testing.' That is essentially the same use as we looked at earlier, which is on 171, the same document, line 28, which is using these reagents as anticoagulants. That is essentially the same thing has just appeared in two places; yes?

A. *Yes, I agree it is essentially the same concept.*

MR. TURNER: *My Lord, I have no further questions....*

MR. PURVIS: *My Lord, I have no re-examination.*

APPENDIX 21

Translation of Dutch Judgment

BMS Holdings Ireland Unlimited Co v. *Sandoz BV*,
(Court of Appeal of The Hague, 15th August 2023).

The Court of Appeal will hereinafter refer to the appellant BMS and to the respondents jointly as Teva et al.

The respondents in both cases will hereinafter be jointly referred to as Sandoz et al.

1. The essence of the case

1.1 In the present proceedings BMS claims, among other things, that Sandoz et al. must be banned from marketing generic apixaban. Among the issues to be discussed is the interpretation of decision G2/2 l dated 23 March 2023 of the Enlarged Board of Appeal (EBA) of the European Patent Office (EPO) and whether the patent which BMS relies on can be deemed to have inventive step in that light.

2. Course of the proceedings before the Court of Appeal

2.1 The course of the proceedings before the Court of Appeal is evidenced by the following documents:

- the notice of expedited appeal with grounds for appeal dated 22 May 2023, by which BMS lodged an appeal against the judgment of the preliminary relief court of the District Court of The Hague dated 17 May 2023 in the case against Sandoz with case number/cause-list number C/09/644989 KG ZA 23-240;
- the notice of expedited appeal with grounds for appeal dated 22 May 2023, by which BMS lodged an appeal against the judgment of the preliminary relief court of the District Court of The Hague dated 17 May 2023 in the case against Stada et al. with case number/cause-list number C/09/644996 KG ZA 23-244;
- the notice of expedited appeal with grounds for appeal dated 5 June 2023, by which BMS lodged an appeal against the judgment of the preliminary relief court of the District Court of The Hague dated 31 May 2023 in the case against Teva et al. with case number/cause-list number C/09/646434 KG ZA 23-322·
- the Sandoz Defence on Appeal, with exhibits;
- the Stada et al. Defence on Appeal, with exhibits;
- the Teva et al. Defence on Appeal, with exhibits;
- the exhibits which BMS submitted for the oral hearing referred to below;
- the exhibits Sandoz submitted for the oral hearing referred to below;
- the exhibits Stada et al. submitted for the oral hearing referred to below; the exhibits Teva et al. submitted for the oral hearing referred to below

2.2 An oral hearing took place on 29 June 2023. The attorneys explained the case based on their memorandums of oral arguments, which they submitted.

3. **Factual background**

3.1 BMS is part of the BMS Group. The BMS Group is a pharmaceutical group of companies with global operations, which is focused on the development of medicinal products. BMS has had a global partnership with Pfizer since 2007.

3.2 BMS markets the medicinal product with the brand name Eliquis®, with apixaban as its active ingredient, in the Netherlands among other countries. Apixaban is a substance that inhibits the effect of factor Xa. Inhibiting factor Xa helps prevent the formation of blood clots. Eliquis® is used in tablet form as an anticoagulant, or blood thinner, in the treatment of thromboembolic disorders.

3.3 Bristol-Meijers Squibb Company (United States) filed an international PCT application under number WO 03/026652 (hereinafter "WO 652") entitled *"Lactam-containing compounds and derivatives thereof as factor Xa inhibitors"* on 17 September 2002. The application relies on the priority document US 60/324165 dated 21 September 2001 (hereinafter: US 165).

3.4 WO 652 was continued as a European patent application and was ultimately granted under publication number EP I 427 415 BI (hereinafter "EP 415" or the "Patent"), with BMS as the patent holder, on 12 August 2009. EP 415 was valid in the Netherlands, among other countries, up to and including 16 September 2022.

3.5 EP 415 is the basic patent for Supplementary Protection Certificate (NL) 300500 for "Apixaban in the form of a pharmaceutically acceptable salt, if so required" (hereinafter the "SPC"). The SPC entered into effect on 17 September 2022 and is valid up to and including 19 May 2026.

3.6 In the authentic English version, claims 1-4 of EP 415 as relied on read as follows:

> 1. A compound, which is represented by formula (1) [apixaban - Court of Appeal]
>
> [Diagram not included in judgment]
>
> or a pharmaceutically acceptable salt thereof.
>
> 2. A compound according to claim 1, which is represented by the formula (I).
>
> 3. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of the formula (I) of claim I or a pharmaceutically acceptable salt thereof.
>
> 4. A pharmaceutical composition, comprising: the pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 2.

3.7 The international patent application WO 00/39131 (hereinafter "WO 131") dated 17 December 1999 is the closest prior art for EP 415. WO 131 was published on 6 July 2000 and is entitled *"Nitrogen containing heterobicycles as factor Xa inhibitors".* The inventors belong to the same research group as the inventors of EP 415.

3.8 During the examination procedure EP 415 was limited to apixaban, following objections by the Examiner of the EPO against a main claim he considered to be too broad (a Markush formula). At the request of the Examiner, as evidence for BMS's claim that apixaban is a more potent

factor Xa inhibitor than the compounds in WO 131 that are structurally the closest, BMS submitted the results of in vitro tests during the examination procedure.

3.9 By summons of 2 July 2021, Teva Nederland B.V. initiated proceedings before the District Court of The Hague under the accelerated regime in patent cases *(versneld regime in octrooizaken* or VRO) against BMS, seeking the revocation of the Dutch part of EP 415 and the SPC (hereinafter the "YRO proceedings"). These proceedings were stayed, pending the EBA's decision in case G2/21.

3.10 Sandoz is part of the Sandoz Group, which is engaged in the development, production and distribution of, among other things, generic medicinal products. One such medicinal product is the generic version of Eliquis (hereinafter "apixaban Sandoz").

3.11 Sandoz obtained marketing authorisations for apixaban Sandoz 2.5 mg and 5 mg film-coated tablets on 24 September 202 I. Sandoz had apixaban Sandoz included in the G-standard of May 2022, which was published on 12 April 2022. Apixaban Sandoz has become a preferred medicinal product for several health insurers.

3.12 In response to the inclusion of apixaban Sandoz in the G-standard, BMS instituted preliminary relief proceedings against Sandoz in April 2022. A judgment was rendered in that case on I0 May 2022. The preliminary relief court assumed that there was a substantial chance that the patent and the SPC would not be upheld in proceedings on the merits due to a lack of inventive step, merits and therefore denied an injunction. Briefly put, he held that the improved inhibition of factor Xa by a Ki value in the nanomolar range asserted by BMS could neither be inferred from, nor had been made plausible in the original application, so that this effect could not be taken into account in assessing inventive step.

3.13 Stada et al. are part of the Stada Group, which is engaged in the development, production and distribution of mainly generic medicinal products. One such generic medicinal product is Apixaban CF. Apixaban CF is a generic version of Eliquis®.

3.14 Stada et al. obtained marketing authorisation for Apixaban CF 2.5 mg and 5 mg on 3 January 2022. Stada et al. announced on 7 March 2023 that this product would be included in the May 2023 G-standard on 18 April 2023 and that it would enter the market on 1 May 2023.

3.15 Teva et al. are part of the Teva Group, which is engaged in the development, production and distribution of, among other things, generic medicinal products. One such medicinal product is the generic version of Eliquis (hereinafter "apixaban Teva").

3.16 Teva B.V. obtained marketing authorisations for apixaban Teva on 17 November 2020. In a letter dated 18 April 2023 Teva et al., or their attorney, wrote to BMS and informed it that they intend to market their generic product apixaban in the near future. Teva had apixaban Teva listed in the G standard for June on 16 May 2023.

3.17 On 23 March 2023, the EBA issued a decision in case G 2/21. The following questions were submitted to the EBA:

> *1. If for acknowledgement of inventive step the patent proprietor relies on a technical effect and has submitted evidence, such as experimental data. to prove such an effect, this evidence not having been public before the filing date of the patent in suit and having been filed after that date (post-published evidence): 1 Should an exception to the principle of free evaluation of evidence (see e.g.* G *3/97, Reasons 5, and* G *1/ 12.*

Reasons 31) be accepted in that post-published evidence must be disregarded on the ground that the proof of the effect rests exclusively on the post-published evidence?

2. If the answer is yes (the post-published evidence must be disregarded if the proof of the effect rests exclusively on this evidence), can the post-published evidence be taken into consideration if. based on the information in the patent application in suit or the common general knowledge, the skilled person at the filing date of the patent application in suit would have considered the effect plausible (ab initio plausibility)?

3. If the answer to the first question is yes (the postpublished evidence must be disregarded if the proof of the effect rests exclusively on this evidence), can the postpublished evidence be taken into consideration if. based on the information in the patent application in suit or the common general knowledge, the skilled person at the filing date of the patent application in suit would have seen no reason to consider the effect implausible (ab initio implausibility)?

3.18 Before answering these questions, the EBA considered the following, among other things:

70. The Enlarged Board takes note of the classification done by the referring board in respect of the case law of the boards of appeal concerning the relevance of post-published evidence to prove an asserted technical effect for acknowledgement of inventive step (see points 13.4 to 13.6 of the Reasons for the referring decision).

71 However, when analysing the case law in more detail and irrespective of the conceptual terminologies for what questions 2 and 3 refer as two distinct plausibility approaches the Enlarged Board understands from the case law of the boards of appeal as common ground that the core issue rests with the question of what the skilled person. with the common general knowledge in mind. understands at the filing date from the application as originally filed as the technical teaching of the claimed invention.

72 Applying this understanding to the aforementioned decisions, not in reviewing them but in an attempt to test the Enlarged Board's understanding, the Enlarged Board is satisfied that the outcome in each particular case would not have been different from the actual finding of the respective board of appeal. Irrespective of the use of the terminological notion of plausibility, the cited decisions appear to show that the particular board of appeal focused on the question whether or not the technical effect relied upon by the patent applicant or proprietor was derivable/or the person skilled in the art from the technical teaching of the application documents.

87 Notwithstanding the/act that the aforementioned decisions were taken on the decisive facts of the case in hand and the particular submissions made by the parties to those proceedings, the Enlarged Board recognises a certain degree of common ground that the courts of the EPC Contracting States, when confronted with the examination of an asserted technical effect in the assessment of inventive step and with the question whether a patent proprietor may rely on post- published evidence to confirm that technical effect, ponder on the technical teaching of the claimed subject-matter that the person skilled in the art, with the common general knowledge in mind, understands from the patent application.

3.19 The "concluding considerations" about questions 2 and 3 that preceded the Order read as follows*:*

92. The term "plausibility" that is found in the case of the boards of appeal and relied upon by the referring board in questions 2 and 3 of the referral and the reasons for it, does not amount to a distinctive legal concept or a specific patent law requirement under the EPC, in particular under Article 56 and 83 EPC. It rather describes a generic catchword seized in the jurisprudence of the boards of appeal, by some national courts and by users of the European patent system.

93.The relevant standard for the reliance on a purported technical effect when assessing whether or not the claimed subject-matter involves an inventive step concerns the question of what the skilled person, with the common general knowledge in mind. would understand at the filing date from the application as originally filed as the technical teaching of the claimed invention. The technical effect relied upon, even at a later stage. needs to be encompassed by that technical teaching and to embody the same invention, because such an effect does not change the nature the claimed invention.

94.Hence, a patent applicant or proprietor may rely upon a technical effect/or inventive step if the skilled person. having the common general knowledge in mind, and based on the application as originally filed, would consider said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention.

95.The Enlarged Board is aware of the abstractness of some of the aforementioned criteria. However, apart from the fact that the Enlarged Board. in its function assigned to it under Article 112(1) EPC, is not called to decide on a specific case, it is the pertinent circumstances of each case which provide the basis on which a board of appeal or other deciding body is required to judge. and the actual outcome may well to some extent be influenced by the technical field of the claimed invention. irrespective of the actual circumstances of a particular case, the guiding principle set out above should allow the competent board of appeal or other deciding body to take a decision on whether or not post-published evidence may or may not be relied upon in support of an asserted technical effect when assessing whether or not the claimed subject-matter involves an inventive step.

3.20 The EBA then answered the questions submitted as follows in its *'Order'*

I Evidence submitted by a patent applicant or proprietor lo prove a technical effect relied upon/or acknowledgement of inventive step of the claimed subject-matter may not be disregarded solely on the ground that such evidence, on which the effect rests, had not been public before the filing date of the patent in suit and was filed after that date.
II A patent applicant or proprietor may rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention.

3.21 Several revocation proceedings are pending against foreign parts of EP 415. Sandoz Limited and Teva Pharmaceutical Industries Limited brought revocation proceedings against BMS in the United Kingdom. On 7 April 2022, Meade J of the High Court ruled that the English part of EP 415 is invalid due to a lack of plausibility and technical contribution. On 4 May 2023, the England and Wales Court of Appeal (Civil Division) affirmed Meade J.'s decision. Invalidity proceedings are also pending in Bulgaria, Denmark, Finland, Hungary, Ireland, Italy, Croatia, Poland, Portugal, Slovakia, Spain, the Czech Republic and Switzerland. In all these countries, Teva companies are parties to the proceedings.

3.22 In France, Norway and Sweden judgments on the merits have already been rendered. In all those proceedings, the Teva companies' objections against lack of inventive step were dismissed and the relevant national part of EP 415 was found valid.

3.23 An injunctive measure was recently imposed on Teva companies, as preliminary relief, in proceedings in Finland and Ireland.

3.24. In the United States, Canada and Korea, BMS successfully defended the validity of the relevant national patents equivalent to EP 415, and the generic versions of Eliquis® were held to be infringing.

4. Proceedings before the District Court

4.1 BMS summoned Sandoz et al. - in separate proceedings and, in Sandoz' view: again - and (briefly put) brought a claim for an infringement injunction, an order to remove generic apixaban form the G standard or have it removed, an injunction against unlawful acts by inciting infringement, with ancillary claims (listing, recall and rectification), all this subject to a penalty and immediately enforceable regardless of appeal, ordering Sandoz et al. to pay the full costs of the proceedings on the basis of Article 1019h of the Dutch Code of Civil Procedure (hereinafter the "DCCP").

4.2 To substantiate its claims, BMS asserted - briefly put - that Apixaban Sandoz, Apixaban CF and Apixaban Teva each satisfy the features of claims 1 through 4 of EP 415 and also fall under the SPC. For Stada et al. and Teva et al. the inclusion in the G standard formed a substantial threat of direct infringement - or of unlawful acts against BMS - making BMS entitled to and have an interest in the preliminary measures.

4.3 Sandoz et al. have put forward a defence seeking dismissal of BMS's claims.

4.4 The preliminary relief court dismissed the claims in all proceedings and ordered BMS to pay the costs of the proceedings. In short, the preliminary relief court upheld Sandoz et al.'s defence and ruled that EP 415 concerns a selection invention because it protects a compound that had already been disclosed in WO 131 as being one of the possible outcomes of the Markush formulas described therein. The original application (WO 652) did not provide plausible reasons for the technical effect of apixaban, let alone a surprising effect compared to the group of compounds disclosed in WO 131. On the basis of the foregoing the preliminary relief court ruled that the patent and the SPC based thereon had a substantial chance of not surviving revocation proceedings.

5. Claims on appeal

5.1 BMS lodged an appeal because it did not agree with the Judgment. It brought several grounds for appeal against the Judgment. BMS brings the same claims it brought before the preliminary relief court. In addition to this, it claims that security must be provided pursuant to Article 233(3) DCCP in case the Court of Appeal is to find immediate enforceability regardless of appeal inadmissible without further conditions. As a second alternative, BMS claims that if its claims for injunction are dismissed that the continued marketing of generic apixaban should be subject to a security pursuant to Article 70(11) of the Dutch Patents Act 1995.

5.2 In short, BMS's claims pertain to the preliminary relief court's interpretation of the G2/21 decision rendered by the EBA.

5.3 Sandoz et al. raised broadly similar defences to BMS's claims for injunction. Only Teva et al. additional argued that EP 415 is not valid because the BMS company that relied on the priority right was not the company that was entitled to do so. Teva et al. argue that EP 415 is invalid in part because of this ground, since the prior art after the priority date is prejudicial to novelty.

6. The assessment on appeal

6.1 Central to the present proceedings is the question of which criteria must be tested in the context of the assessment of whether a patent claim involves inventive step.

The inventive step test according to G2/21

6.2 One of the methods used by the EPO to assess the inventive step is the problem solution approach (hereinafter the "PSA"). This method identifies the technical effects of the differences between the features of the patent claim that was granted and the closest prior art. These technical effects are used to identify the objective technical problem, i.e. the problem that must be solved in order to achieve the technical effects. Subsequently it is assessed whether the skilled person (m/f), taking into account their common general knowledge on the priority date, *would* arrive at the solution presented in the patent (the features of the patent claim) without inventive step.

6.3 The formulation of the objective technical problem is therefore closely related to the technical effects achieved with the invention (relative to the closest prior art). The EBA considered, among other things, in G2/21:

25. The technical problem must be derived from effects directly and causally related to the technical features of the claimed invention. An effect could not be validly used in the formulation of the technical problem if the effect required additional information not at the disposal of the skilled person even after taking into account the content of the application in question (see CLB, 10th edition, .I.D.4. I, and the decisions therein).

26. Step {c) [in de PSA, namelijk 'determining the technical effect(s) or result(s) achieved by and linked to the difference{s) between the subject-matter of the claim at issue and the disclosure of the closest prior art - hof]. *which is the most relevant in the context of the present referral, requires that, in order to determine the objective technical problem, the technical results and effects achieved by the claimed invention as compared with the closest prior art must be assessed. According to the established case law of the boards of appeal(. ..) it rests with the patent applicant or proprietor to properly demonstrate that the purported advantages of the claimed invention have sucessfully been achieved.*

6.4 The importance of G2/2 l lies - in part - in the fact that the EBA has ruled when a patent proprietor may rely on the technical effect achieved by their invention in the context of the assessment of its inventive step these being

"if the skilled person, having the common general knowledge in mind. and based on the application as originally filed. would derive said effect as·being encompassed by the technical teaching and embodied by the same originally disclosed invention".

Interpretation ofG2/21

6.5 Sandoz et al. argue that the test formulated in G2/21 means that when assessing the inventive step, any claimed technical effect may only be relied upon if the skilled person can already understand from the patent application that the claimed effect is actually achieved by the invention and that this actually solves the problem, or at least that such is made plausible. This position is rejected.

6.6 The Court of Appeal agrees with BMS that the only requirement imposed by G2/2 l for being allowed to take into account a technical effect - as established when using the PSA on the basis of a comparison between the invention disclosed in the patent and the closest prior art - when formulating the objective problem and assessing the inventive step on the basis of this problem, is that the skilled person, using their common general knowledge on the priority date, can derive from the patent application that the claimed technical effect is encompassed by the technical teaching, and embodies the same invention disclosed in the patent application.

6.7 The Court of Appeal notes in that respect that, in light of the considerations in the G2/21 decision, the words "would derive" in paragraph II of the Order - the definition of which the parties disagree on - do not mean anything else than "derivable" according to the aforementioned decision. Cf. in that context the "intermediate conclusion" in paragraphs 70 through 72 of G2/21 (cited in para. 3.18 above).

6.8 The EBA's considerations in G2/21 entail that the test according to G2/21 does not require for the assessment to have the patent application already include evidence that the claimed technical effect actually occurs or that such is made plausible in this application, as argued by Sandoz et al. In paragraph 74 of G2/21 the EBA pointed out that the inventive step and sufficiency of disclosure, as well as its assessment, must be clearly treated as separate and on their own merits: *"the issues of sufficiency of disclosure (Article 83 EPC) and inventive step (Article 56 EPC) and their assessment are clearly to be treated separately and on their own"*

6.9 In that context, the EBA held in paragraph 77 of G2/21 that the possibility of relying on "postpublished evidence" to demonstrate that the claimed effect actually occurs is a lot more limited for the assessment of the sufficiency of disclosure when compared to the assessment of inventive step. For an invention that includes the technical effect achieved in the claim, such as the therapeutic effect in the case of a second medical indications claim, such evidence may only be considered if the evidence for the claimed effect is already included in the application, especially if the occurrence of this effect is not made credible due to a lack of experimental data. The preliminary opinion is that this consideration is incompatible with G2/2 l being interpreted as the assessment of the inventive step being subject to the condition that the claimed effect must always have been made plausible in the application, as argued by Sandoz et al.

6.10 It also follows from this that "technical teaching" is not understood to include "that which is taught to the ski lied person, *on the basis of the information included in the application,* with regard to how the technical problem *can actually be solved* with technical means" (as incorrectly argued by Sandoz et al. paragraph 63 of the HB oral arguments). As BMS correctly argues, the technical teaching of a patent must be understood to mean "that which is taught to the skilled person with regard to how the technical problem can be solved with technical means"[1]

Cf. GI/ 19, paragraph 24, with reference to the "Basic proposal for the revision of the European Patent Convention, MR/2/00, Munich, 13-10-2000, p. 43": "technical teaching, ie an instruction addressed to a skilled person as to how to solve a particular technical problem using particular technical means".

6.11 lf the test of G2/2 I has been met, during the grant of the patent the patent proprietor may then present further evidence that the claimed effect actually occurs (cf. paragraph 26 of G2/21 last

sentence). lf that evidence is provided, the effect may then be included in the assessment of the inventive step.

6.12 Contrary to Sandoz et al.'s arguments, this interpretation of G2/21 by the Court of Appeal does not give licence for speculative patents. The granting of protection on the basis of a purely speculative patent for an invention that will only be made after the fact is avoided through the requirement that the technical effect must already be encompassed by the technical teaching of the application and embodies the same invention that is disclosed in the application. Moreover, it is well established that EP 415 is not a speculative patent. BMS undisputedly argued that the inventors had already established the favourable affinity and selectivity of apixaban through trial and error prior to filing the patent application.

6.13 The Court of Appeal may leave it open to interpretation whether and to what extent the G2/21 test is different from the test used in Dutch case law. While the Dutch courts - as well as the courts in other countries that are party to the European Patent Convention - are not bound by decisions of the EBA, these decisions are generally considered to be authoritative, and are usually followed. indeed, the decisions of the EBA are intended to promote the uniform application of the law that is applicable to the validity of European patents, as laid down in the European Patent Convention and as included in the national legislations of the countries that are party to that convention. Compliance with the decisions of the EBA therefore contributes to the desired harmonisation of patent law and its application in the countries that are party to the convention. The Court of Appeal will therefore use the test formulated by the EBA in G2/21.

Does EP451 pass the inventive step test according to G2/21?

6.14 The EBA indicated in paragraph 95 of G2/2 l that the "rather abstract" criteria established in G2/2 l must be *interpreted* for a specific case on the basis of the specific circumstances of this case. This involves establishing the requirements for the skilled person to derive from the application that the claimed technical effect was encompassed by its technical teaching. This depends on the specific circumstances of the case. It is not inconceivable that in some cases this may require, for example, that test results or scientific teaching is disclosed in the application. The Court of Appeal points out that this does not necessarily involve a stricter requirement (within the meaning of a different test) but that the skilled person needs more to meet the requirements of the G2/2 l test under the given circumstances. This assessment- the actual interpretation of the G2/2 l criteria based on the specific circumstances of the case - can therefore be distinguished from (plausible) evidence always being required in the application that the technical effect actually occurs before post-filed evidence can be considered, as incorrectly argued by Sandoz et al

6.15 ln this case it is important for the assessment of whether the criteria provided by G2/21 are met that the application expressly and specifically designates the relevant effect as the primary objective of the patent. The technical effect achieved with the patent, which BMS relies on, is an improved factor Xa inhibition. As rightly pointed out by Sandoz et al., "improved" must be considered to be "improved in relation to the compounds disclosed in WO 131 ". This effect is stated in the following passage of the application, describing the objective of the invention in relation to the prior art described above this passage, including WO 131 (WO 652, p. 6):

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors. In addition, it is also desirable to find new compounds with

improved pharmacological characteristics compared with known factor Xa inhibitors. For example, it is preferred to find new compounds with improved factor Xa inhibitory activity and selectivity for factor Xa versus other serine proteases (i.e., trypsin). It is also desirable and

6.16 Other than in cases in which the plausibility of an effect was in dispute (for example, TBA 10 April 2019, T 235/13, Nakao, and Court of Appeal of The Hague 7 November 2017, ECLI:NL:GHDHA:2017:4029, Leo Pharma/Sandoz), it does not need to be assessed whether the skilled person would recognise the claimed effect in the application on the basis of their common general knowledge.

6.17 Moreover, this case differs from cases in which the scope of the claim caused the skilled person to doubt whether the application teaches that the claimed effect can be realised for the full scope of the claim in the patent (for example, TBA 12 September 1995, T 0939/92, AgrEvo). This is because the claims in EP 415 do not cover large groups of compounds but only one specific compound, this being apixaban. Sandoz et al. also did not argue that the skilled person would deem the alleged effect of the claimed compound implausible on the basis of their common general knowledge (as was the case in TBA 28 June 2005, T 1329/04, Johns Hopkins).

6.18 Furthermore, it is important to note that it is established between the parties that the application discloses a test that the skilled person can use to easily verify the favourable Ki value of apixaban and thus its claimed effect.

6.19 The preliminary opinion is that these circumstances, when considered together, entail that the skilled person with their common general knowledge on the priority date would derive from the application a technical teaching entailing that the claimed effect can be achieved with apixaban if the skilled person can derive from the application that apixaban is a promising candidate in this regard. According to BMS, this can be derived from the application for the following reasons.

6.20 The common general knowledge of the skilled person to be considered is uncontested.

6.20.1 Factor Xa inhibition is a more effective and safer route than thrombin inhibition. One factor Xa molecule generates thousands of thrombin molecules.

6.20.2 Du Pont was working on the development of factor Xa inhibitors.

6.20.3 Factor Xa inhibitors with Ki values had already been identified in the nanomolar range. These had not yet been developed clinically due to insufficiently advantageous pharmacokinetic properties.

6.20.4 After a factor Xa inhibitor is identified in a research project, the next step is in vitro testing for factor Xa inhibition as well as other serine proteases for selectivity.

6.20.5 Such in vitro tests are easy to set up (commercial kits were already available for factor Xa and other enzymes in 2001), quickly take effect and are easy to monitor.

6.20.6 The next step is to do an "oral bioavailability' test. This requires an amount of 1 to 50 mgs.

6.20.7 The follow-up step, animal testing, again needs a bigger amount.

6.21 BMS is of the opinion that the skilled person, with the above common general knowledge in mind, would read the following in the application:

6.21.1 that the objective is to develop effective factor Xa inhibitors with improved factor Xa inhibition, selectivity and other pharmacological properties (see the passage cited above (WO 652, p. 6);

6.21.2 that with regard to the Xa inhibition, compounds were sought with a nanomolar or subnanomolar effect and a Ki value under 0.001 μM, which is the preferred range mentioned in WO 652;

6.21.3 that the application discloses an easy-to-perform test to determine the Ki value;

6.21.4 that the inventors were looking for improved factor Xa inhibitors and found them in the form of lactam-containing compounds. The skilled person would derive this from the title of the application: "Lactam-containing compounds and derivatives thereof as factor Xa inhibitors", the "Summary of the invention", which is entirely about lactam-containing compounds as factor Xa inhibitors and the "Background of the invention". That paragraph is entirely about factor Xa inhibition and explains how factor Xa inhibition works and that this approach is more effective than thrombin inhibition:

> Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to
> generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, CA^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, s., Varadi, K.: Optimization of conditions Complex: Probable role of the complex in the amplification of blood coagulation. *Thromb. Res.* 1979, *15,* 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

6.21.5 that the skilled person would derive from "Accordingly" that the inventors achieved the set objective by developing lactam-containing compounds. The skilled person would interpret "useful" as meeting the stated purpose in light of the objective:

> SUMMARY OF THE INVENTION
> Accordingly, the present invention provides novel lactam-containing compounds and derivatives thereof that are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

6.21.6 that lactam-containing compounds have been synthesised and tested, according to WO 652 (p. I 68, 1. 15 - p. 170 I. 20);

6.21.7 that the skilled person would infer from example 18 that apixaban has been synthesised on a much larger scale than the other lactam-containing compounds that have been synthesised, in a quantity and purity (after two recrystallisation steps) that is sufficient for use in animal testing;

6.21.8 that apixaban is specifically claimed in claim 8.

6.22 The Court of Appeal is of the preliminary opinion that BMS rightly argues that the skilled person can use all this to derive from WO 652 that apixaban is the most promising factor Xa inhibitor. In view of the findings of the Court of Appeal in para. 6.19, the G2/21 test has been passed.

6.23 This is confirmed by the outcome of proceedings on the merits abroad.

6.24 In the French and Norwegian proceedings, the Teva companies brought roughly the same objections and defences against the inventive step opposing BMS's aforementioned position as were brought in the present proceedings. These objections and defences were dismissed and BMS's patent was deemed valid in both proceedings on the merits. In summary, both the French and Norwegian courts hearing the case on the merits held that the skilled person, using their common general knowledge on the priority date, could derive from the application that the objective of finding a compound with an improved factor Xa inhibition, selectivity and pharmacological properties compared to the factor Xa inhibitors that are already known could be achieved with apixaban and that this could then be, indisputably, proven with post-filed evidence.

6.25 The findings made in the French judgment in this regard include but are not limited to the following (in an uncontested English translation provided by BMS):

> 54. The Court notes, however. that the initial filing specifically discloses apixaban (page 76 of the translation of Document WO'652), which is further exemplified (no. 18). admittedly among 140 examples and a description of over 100 product summaries.
>
> 55. However, the Court notes that this Document WO'652 reveals tests, resulting in the determination of the *"most preferred'* compounds with very high affinity and in particular Ki ≤ 0.001µM. This Document WO'652 further specifies that the invention relates to a factor Xa inhibitor whose pharmalogical and pharmacokinetic properties arc improved. It further describes that 3.07 g of apixaban have been synthesized (page 178). This quantity undoubtedly distinguishes apixaban among all the examples of synthesised compounds, in that it is, by far, the largest quantity synthesized by the description (no other example falls to the gram, with the other largest quantity synthesized being Example 91: 034g)
>
> 56. A person skilled in the art would have necessarily deduced, on the basis of common general knowledge, that the patentee thought that apixaban was a promising compound, or even the most promising compound[3]

[3] It is also the conclusion that the English decision reached (items 171 and 172 of the High Court of England and Wales judgment of 7 April 2022: "The 3g point is not completely without relevance (…) it sets apixaban apart from the other exemplified compounds based on information in '652 itself that I think the skilled reader would notice. However () I do not see how the point can go any further than the patent thought that apixaban was promising.)

> 57. Of course. this conclusion is not formally expressed in the description from the priority date and is further less corroborated by data made public in this document when it was filed.
>
> 58. However, such a requirement for disclosure of results does not appear in the EPC. neither in the implementing regulation, nor in French case law for a patent other than a second therapeutic application (for it to be sufficiently described), whereas in this case, the extent of patent EP'415 monopoly corresponds to apixaban (regardless of its therapeutic application).

59. As it has been seen. the technical effect of apixaban is also credible from the point of view of a person skilled in the art when reading the patent specification a filed (it being noted that the protection of third parties is in principle ensured through the complaint of undue extension). As a result, it does not appear to be justified here to deprive BMS from the possibility of providing proof of the contribution of this compound to the state of the art., on the date of filing, by the production of external and contemporary elements.

60 In this case, BMS submits to the proceedings the laboratory notebooks and reports of its researchers. prior to the filing of the WO'•652 application, which indisputably demonstrate in a manner that has actually not seriously been disputed. that it was in possession of the invention, i.e. a factor Xa inhibitor. useful in treating thromboembolic disorders. \\ith improved pharmacological and pharmacokinctic properties.

6.26 The findings made in the Norwegian judgment in this regard include but are not limited to the following:

Further reference is made to the patent application page 170. lines 21 to 22 (FU page 1779) where it is stated that: "Compounds tested in the above assay are considered to be active if they exhibit a Ki of ≤10 μM." Furthermore. more preferred values of Ki ,are listed before it is stated that: "Still more preferred compounds of the present invention have Ki's of ≤0.001 μM" in line 26. Thus. it is explicitly stated from the application that the most preferred compounds are potent factor Xa inhibitors.

The skilled person would understand that the substance produced had been tested in the normal way, and that several of the substances had proved to be effective factor Xa inhibitors. Furthermore. the skilled person would understand that the compound in example 18 apixaban had been selected for further study because it had yielded promising results in initial tests. as an effective factor Xa inhibitor.

The skilled person would note that apixaban is the only compound produced in a large amount. Of all the example in WO 652. quantities from l to 424 mg haw been produced, with the exception of example 18.which is apixaban, where 3070 mg (3.07 grams) is produced. The skilled person would have noted the large amount of 3.07 grams . Apixaban was not only produced in a large amount. but was subjected to further purification and recrystallization steps. These are steps necessary for the preparation of a pure: material for further pharmacokinetic studies and preclinical development studies of potential drug

The court notes that the synthesizing process in example 18 consists of six synthesis steps, with an overall low yield of 1.3%. This is a demanding process, where intermediate products were produced several times. It is often more demanding to produce larger quantities of chemical substances than smaller ones. The skilled person would understand that the manufacture must have been based on a deliberate process, and that example 18 (apixaban) was the most promising substance, and that animal experiments were probably planned or carried out in vivo with this substance. Thus, it is plausible to the expert that apixaban had a sufficiently good selectivity to study the antithrombic effects in vivo.

Following this, it is the court's view that the skilled person would consider apixaban to be a credibly effective factor Xa inhibitor.

It is then permissible to rely on subsequent evidence. It is agreed that subsequent evidence confirms the effect.

The objective technical problem can thus be formulated as: to produce an effective factor Xa inhibitor for the treatment of thromboembolic disorders, with improved properties.

6.27 As recalled in the French judgment (footnote 3 to para. 56 of that judgment), the English court *de facto* ruled that the skilled person would notice the synthesis of apixaban at gram-level and that they would infer from this that the inventors regarded apixaban as "promising". The fact that the outcome of those proceedings was nevertheless different lies in the fact that the English High Court and Court of Appeal are bound by the English Supreme Court precedent in the Warner-Lambert v Generics proceeding [2]. On this basis, the application requires a scientific substantiation or test results which make it plausible for the claimed technical effect to occur. The English court was of the opinion that that test had not been passed: "/ *do not see how the point can go any farther than that the patentee thought that apixaban was promising. A bare assertion to that effect in '652 (bare in the sense of lacking data or reasoning) would not have been any use in establishing plausibility, as is clear from the second point in [37] in Warner-Lambert."* (UK High Court [2022] EWHC 822 (Pat) par. 172).

6.28 The Court of Appeal is of the preliminary opinion that the test applied by the English court- which Sandoz et al. defend in the present proceedings - is a different test than the test applied in paragraph II of the Order in G2/2 I. The English test was developed by the English Supreme Court in a case regarding the sufficiency of disclosure and not inventive step. For the sufficiency of disclosure of second medical indications claims the EBA formulated a different test in paragraph 77 of G2/21 than the one formulated in paragraph 11 of the Order. As already held above in para. 6.9, the Court of Appeal does not consider it compatible with that finding to apply the same test when assessing the inventive step of a claim that does not include the technical effect to be achieved, as is the case for the substance claim.

6.29 The test applied by the Swedish court also implies that the invention must be derivable the application (judgment p. 29, third paragraph)

The Patent and Market Court initially states that the technical effect must be derivable from the patent application, either directly or through the general knowledge of the skilled person.

The Swedish court also further ruled that the application is not required to include evidence that the technical effect actually occurs:

According to the court, the skilled person who, with his general knowledge, took part of the patent writing would hold it too probable that apixaban was an fXa inhibitor and in the absence of anything which indicated the opposite would not find grounds for doubt. The mere absence of specific biological data would not have led the skilled person to question the function of apixaban, nor has the investigation in the case revealed anything else that would have given the skilled person reason to doubt the compound's function as an fXa inhibitor.

6.30 During the examination procedure, and therefore only after the application, BMS provided evidence that apixaban is indeed an improved Xa inhibitor in comparison with the compounds that are structurally the closest as disclosed in WO 131. It is not in dispute that this evidence has been provided. The French, Norwegian and Swedish courts have found EP 415 to involve an inventive step.

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[2] Warner- Lambert Company LLC (Respondent) v Generics (UK) Ltd t/a Mylan and another (Appellants) [2018] UKSC 56, par.37

6.31 The Dutch preliminary relief court is not bound by decisions of foreign courts on the merits in disputes on parallel patents, except on the basis of the choice of law regulation for decisions by the Dutch court hearing the case on the merits. However, these decisions do have authority, especially when they largely concern the same facts, arguments and questions of law as is the case for the present proceedings.

6.32 The Court of Appeal deems the decisions rendered by the French and Norwegian courts hearing the case on the merits to be verifiable. This also particularly applies to the opinions in these decisions that- contrary to Sandoz et al.'s arguments - the skilled person, using their common general knowledge on the priority date could derive from the application (cf. paras. 6.20 and 6.21 above) that an *improved* factor Xa inhibitor was sought compared to the Xa inhibitors already disclosed in WO 131, that the individualised substance apixaban disclosed in that application was the most promising candidate for this - and as such means that the application discloses more than a *"mere verbal statement"* of a technical effect-, that there was no reason for the skilled person to doubt that the objective (finding an improved factor Xa inhibitor) could be achieved with apixaban, and that proof of such is not required to be included in the application.

6.33 ln the above proceedings, the parties submitted largely the same arguments as in the present proceedings and both decisions are largely base don the same facts and party expert statements. Sandoz et al.'s view that the skilled person would only interpret WO 131 as searching for an *alternative* factor Xa inhibitor - or at best that the technical effect claimed by BMS of improved Xa inhibition was only published verbatim in WO 131, that it was only disclosed *afterwards* that apixaban was an *improved* Xa inhibitor and that the skilled person would have found this speculative on the priority date in absence of any proof in WO 652 that pointed to such - which is the core of Sandoz et al.'s defence, also in the present proceedings - was dismissed in the present proceedings.

6.34 Taking into account the interpretation of G2/21 above, the Court of Appeal does not see any reason on the basis of Sandoz et al.'s arguments to assume in advance that the outcome of the French and Norwegian proceedings on the merits would be incorrect and that the Dutch court hearing the case on the merits would lead to another outcome.

6.35 Based on all of the above, the Court of Appeal is of the opinion that Sandoz et al.'s defence stating that there is a substantial chance that EP 415 is deemed invalid by the Dutch court hearing the case on the merits due to a lack of inventive step must be dismissed.

6.36 The Court of Appeal thus turns to assess the defences which the preliminary relief court did not address.

Added subject matter

6.37 Sandoz argued (Statement of Defence, paragraph 251) that "to the extent that EP 415 would contain a technical teaching which WO 652 does not (by omission and addition of passages and by limiting the claims), this constitutes added subject matter" without further substantiating this argument.

6.38 The preliminary opinion is that this does not concern added subject matter. As was held above, the Court of Appeals' preliminary opinion is that the Dutch court hearing the case on the merits, in conformity with the French and Norwegian courts hearing the case on the merits, would rule that the skilled person, using their common general knowledge on the priority date, could derive from the application that the objective of finding a compound with improved factor Xa

inhibition, selectivity and pharmacological properties compared to the already known factor Xa inhibitors can be achieved with apixaban. This meets the test requirements of G2/21 (in the context of the assessment of the inventive step) that the claimed technical effect is encompassed by the technical teaching of the application and embodies the same invention disclosed in the application. This case thus does not concern a different technical teaching of EP 415 in relation to that which was disclosed in the application. The substance apixaban claimed in EP 415 was also disclosed in individualised form in the application, both in example 18 and in claim 8.

6.39 Moreover, the Court of Appeal remarks in this regard that BMS rightly argued that if a claim aimed at apixaban had been added at a later point in time, it is not required in the context of the added subject matter that the application makes it plausible or demonstrates that the technical effect claimed in the new claimed invention actually achieves the technical effect. A mere -implicit- disclosure of that which is protected in the new claim is sufficient. This requirement has been met, as demonstrated by the above

Priority

6.40 Teva et al. asserted that the BMS company that invoked the priority of US 165 in the WO 652 application did not have the priority right to do so. This renders the prior art dating after that date prejudicial to novelty and EP 415 invalid.

6.41 The following is established between BMS and Teva et al.

6.41.1 The priority document US 165 was submitted on 21 September 200l by Pinto and Quan, who at that time were employed by DuPont Pharmaceuticals Company (hereinafter DuPont);

6.41.2 DuPont US was acquired by the Bristol-Myers Squibb group, after which the name was changed into Bristol-Myers Squibb Pharma Company (hereinafter also referred to as "BMS Pharma")·

6.41.3 Pinto and Quan transferred their rights to US 165 to BMS Pharma on 3 November 2001;

6.41.4 Bristol-Myers Squibb Company (hereinafter "BMS Company") filed an application for WO 652 for all designated countries, except for the US, on 17 September 2002, stating Pinto and Quan as the inventors and invoking priority on the basis of US 165. For the US, WO 652 was submitted by Pinto and Quan.

6.42 With reference to various statements, BMS advanced that the "beneficial ownership" to BMS Pharma's priority right transferred to BMS Company. Teva et al. did not contest this or, in light of BMS's substantiated statements, at least not in a sufficiently substantiated manner. Nor did Teva et al. advance that pursuant to Article 87 EPC it is not possible for the legal ownership and "beneficial" ownership of the priority right to be held by different companies. Teva et al.'s defence in the present proceedings is mainly based on the assertion that the decisive factor in assessing the right to invoke priority is which party holds the legal ownership and that there was no *transfer* of the *legal* ownership of the priority right by BMS Pharma to BMS Company prior to the WO 652 application.

6.43 In the Court of Appeal's preliminary opinion, BMS's defence comes down to the following. After the acquisition of DuPont, BMS Pharma continued to be the holder of the legal ownership of the priority right and the beneficial ownership was transferred to BMS Company. Having the beneficial ownership, also known as the equitable title, is sufficient to be entitled to exercise priority rights. However, even if this were not the case, here the requirements of Article 87 EPC have in any case been met. A beneficial ownership gives the owner thereof (BMS Company) the

right, under the applicable law of the State of Delaware, to also have the legal ownership transferred by the legal owner (BMS Pharma) on demand. This can be done without specific formalities. By invoking the priority right, BMS Company, as the beneficial owner, implicitly exercised the right to also transfer the legal ownership of BMS Pharma's priority rights. Consequently, in addition to the "beneficial ownership" the legal ownership of the priority right transferred to BMS Company as well. As the Court of Appeal understands BMS's position, it for this reason that it invoked the priority of US 165 in a legally valid manner.

6.44 ln the Court of Appeal's preliminary opinion, this implicit "appropriation" of the legal ownership of the priority rights is in accordance with the agreements made between BMS Pharma and BMS Company in the context of the acquisition of DuPont, namely that BMS Company would file the new patent applications. Consequently for the time being it is sufficiently plausible that pursuant to the agreements in place about which of these companies would file patent applications, both the beneficial and legal ownership of the priority right transferred from BMS Pharma to BMS Company prior to the WO 652 application. In the Court of Appeal's preliminary opinion, this satisfies the requirements set by Article 87 EPC in order for BMS Company being entitled to invoke the priority of US 165. The prior art advanced by Teva et al. dated after that date is therefore irrelevant for the novelty of EP 415.

6.45 In the Swedish and French proceedings on the merits, the Teva companies also invoked a lack of priority, and all the parties put forward largely the same arguments based on largely the same expert statements as in the present proceedings. In both proceedings, the defence of the Teva companies was rejected.

6.46 In the Swedish proceedings, the following was considered in this respect, among other things (p. 21-27 of the judgment):

US 165 was submitted by inventors Donald J. Pinto and Mimi L. Quan. 21 September 2001. The investigation in the case shows that they transferred the said patent application and certain additional rights associated with it to BMS Pharma on 3 November 2001. BMS Pharma has thus taken the place of the inventors as for as US 165 is concerned.

Under the Delaware legal order. a person can be the beneficial owner of property of which someone else is the legal owner. This also applies to inventions and intellectual property rights such as patents. It follows from the said legal order that it is the beneficial owner who has the ultimate decision-making power over the property. It does not require a special transfer from one owner to another for their various interests in the property to arise.

According to the: Patent and Market Court. it is through the statements of Marla Mathias and Paul Golian, which, according to the court, there is no reason to question. that there was a policy within the group regarding the decision-making of intellectual property rights at the time when WO 652 was filed nod that this policy meant that BMS Company had actual control over the rights. Taking into account the internal guidelines and the fact that BMS Pharma was a wholly owned subsidiary - albeit indirectly owned through a subsidiary and a subsidiary - of BMS Company. the court finds that BMS Company at that time was the beneficial owner of US 165.

According to the Patent and Market Court, it is also clear that BMS Company. in the presence of the beneficial owner of US 165, has taken the place of BMS Pharma in the meaning referred to in Article 87 EPC when WO 652 was filed (cf. England and

From the foregoing, it is not shown that BMS Company lacked the right to invoke priority from US 165 when WO 652 was filed.

6.47 The French court hearing the case on the merits arrived at the same conclusion.

> 87. It shall be deducted that BMS Company holds the effective ownership of patent WO'652 as of October 2001 and as such entitled BMS Pharma, so that it has validly filed this application, and validly claimed the priority right attached to the application US' 165.

6.48 Given what was held above, the Court of Appeal sees no reason to assume that the Dutch court hearing the case on the merits will arrive at a different outcome.

Urgent interest

6.49 The Court of Appeal rejects Sandoz et al.'s position that BMS does not have or no longer has an interest in its claims. The circumstance that Sandoz has been on the market with generic apixaban for a long time does not alter the fact that BMS has an urgent interest in its claim. The longer Sandoz continues to offer its generic product at a lower price, the more price erosion will occur. The fact that Sandoz has been on the market with generic apixaban for a longer period of time cannot be attributed to BMS. It acted expeditiously by initiating preliminary relief proceedings. The fact that the preliminary relief court did not maintain the status quo in the first judgment does not mean that BMS no longer has an urgent interest in that situation - i.e. Sandoz no longer being on the market with an infringing product- still being achieved.

6.50 In addition, BMS advanced uncontested that it has an interest in an injunction in the short term, because before the end of this year it still has to negotiate the price agreement for apixaban with the Ministry of Health, Welfare and Sport for the next two calendar years. A relevant factor in this respect is whether generic apixaban is available on the market.

6.51 BMS also has an urgent interest in its claims against Stada et al. and Teva et al. Stada et al. entered the market after the Judgment. Teva et al. has not yet entered the market but *is* included in the G-standard. The expectation is that several generics products entering the market will lead to competition and will strengthen the effect on the negative price spiral already initiated by Sandoz's market entry. Once a drop in prices has been initiated, it is usually irreparable in practice. Moreover, the presence of multiple suppliers of generic apixaban will put further pressure on the aforementioned price negotiations in a way that will negatively affect BMS. This will result in significant damage for BMS. It has an urgent interest in preventing this.

6.52 The circumstance that Teva et al. initiated revocation proceedings against EP 415 does not mean that BMS supposedly no longer has an urgent interest in the present proceedings, as Teva et al. argues. In that case, oral arguments were scheduled for 12 January 2024; Teva et al. did not want to cooperate with the oral arguments being heard simultaneously with the oral arguments in the proceedings scheduled for 13 October 2023 that were initiated by Sandoz. Teva et al. did assert that BMS allegedly had procedural options in those proceeding that remove BMS's interest in being granted relief in preliminary relief proceedings, but did not specify what these supposed options are. Be that as it may, a speedy decision, in which BMS has an interest, was not to be expected in those proceedings. Under those circumstances, BMS was free to seek an injunction in preliminary relief proceedings and to lodge an appeal against the judgment dismissing its claim, also in the event that proceedings on the merits are pending.

Weighing of interests

6.53 Sandoz invoked that the weighing of the interests of the parties in preliminary relief proceedings should be in its favour, and that an injunction should therefore not be imposed. To that end, it

points out that it has been on the market with generic apixaban since the first judgment and that a judgment on the merits will be rendered in the near future. Taking into account BMS's considerable interests in maintaining its SPC and the irreparable price erosion caused by the presence of a cheaper generic product, the Court of Appeal, taking all circumstances into consideration, deems Sandoz's arguments insufficient to reject BMS's injunction.

6.54 In the Court of Appeal's preliminary opinion, Sandoz infringed a valid patent of BMS and is now infringing a valid SPC. Sandoz chose not to initiate revocation proceedings against EP 415 before it entered the market, apparently further to the English High Court's judgment on the merits, despite its previous statement that it would wait until the SPC's expiration. It did this with the knowledge that the EBA would render a decision in G2/21 that could potentially have consequence for the assessment of EP 415's inventive step by a Dutch court. It then stayed on the market even after the EBA had rendered its decision. In doing so, it accepted the risk that after the decision in G2/21 a different ruling could be rendered about the inventive step on appeal or in new preliminary relief proceedings, after which it would have to withdraw its generic apixaban from the market again, with all the related adverse consequences it described - including not being able to meet contractual obligations towards insurers which Sandoz has undertaken and the loss of its 'First mover' advantage.

6.55 This risk has materialised, as the Court of Appeal is of the preliminary opinion that Sandoz should not have placed its product on the market. Under the given circumstances, the adverse consequences for Sandoz of a claim for injunction must remain for its own risk, in the sense that these cannot bring about that the weighing of interests must be to BMS's disadvantage. The circumstance that patients and pharmacists would be disadvantaged if they continuously have to switch between apixaban products is, be that a it may, a circumstance Sandoz - as well as the health insurers that designated apixaban Sandoz as preferred - should have taken into account before it started offering its generic product even during EP 415's term of validity. That is not a circumstance that can be held against BMS, and does not mean that the weighing of interests should be to its disadvantage.

6.56 The fact that proceedings on the merits are currently pending does not mean that the weighing of interests should have a different outcome either. The oral hearing will not take place until 13 October 2023, and a decision therein is therefore not to be expected in the short term. As was held above in para. 6.50, BMS argued, without being contested, that it has an interest in an injunction in the short term in relation to the upcoming price negotiations for apixaban. The Court of Appeal is of the preliminary opinion that there is furthem10re no substantial chance that the court hearing the case on the merits will deem EP 415 invalid.

6.57 Stada et al. entered the market after the Judgment. At the time of the oral hearing in these appeal proceedings Teva et al. was not yet on the market, but it has announced its intention to enter the market. Stada et al., - and Teva et al. in so far as it entered the market prior to this judgment being rendered - thus intentionally accepted the risk that the Judgment would not be upheld. There are no reasons why the materialisation of that risk and the loss or harm resulting from the fact that the parties had to withdraw their product from the market should not remain for their own risk. Nor can the fact that Sandoz has already entered the market with a generic product be to the advantage of Stada et al. and Teva et al. in that weighing of interests. Leaving aside the fact that the Court of Appeal will impose an injunction on Sandoz, and for that reason alone the competition with Sandoz sought by Stada et al. and Teva et al. will not be at hand, a competitor's presence on the market with an infringing product cannot give others a license to enter the market with a different infringing product. Furthermore, in the Court of Appeal's preliminary opinion, the assertion that several suppliers of generic products entering the market will be only to the detriment of Sandoz's market share and not the one of BMS is incorrect. Competition

between various suppliers of generic products will result in an increased negative effect on the price, including for BMS.

6.58 The unilateral Letter of Guarantee issued by Stada et al. to cover the harm or loss to be suffered by BMS, and Sandoz's willingness to issue a similar guarantee, is insufficient to refrain from imposing an injunction, if only in view of the unreasonable limitations regarding the guaranteed amount and its period of validity included therein.

6.59 Teva et al.'s reliance on Article 16 of the Charter (freedom to conduct a business) cannot help it. As Teva et al. recognises, this must be weighed against other rights, such as the rights - protected by Article 17(2) of the Charter - that BMS derives from the SPC. Under the given circumstances, it is not the case that an injunction to be imposed on Teva et al. to enter the market with its generic apixaban product would be a disproportionate measure. In the Court of Appeal's preliminary opinion, the SPC must be deemed valid and an injunction will be imposed on Sandoz and Stada et al. as well Therefore, there is no unjustified prejudicing of Teva et al.'s competitive position compared to these competitors.

Abuse of procedural law?

6.60 Under the given circumstances, Sandoz did not advance sufficient grounds based on which it can be assumed that BMS is allegedly abusing the law or acing contrary to due process by initiating second preliminary relief proceedings. The outcome of the present proceedings confirms that BMS by no means acted "against better judgment".

6.61 BMS was free to request a disciplinary measure again in preliminary relief proceedings, after the EBA had rendered a judgment in G2/2 I and had expressed its opinion therein about a *"point of law of fundamental importance"* that is at hand here (cf. G2/21, paragraph 15). This is not precluded by the fact that BMS did not lodge an appeal against the previous judgment in preliminary relief proceedings, given that a judgment in preliminary relief proceedings does not have res judicata effect. The fact that Sandoz has been on the market for a longer period of time does not alter the assessment either. After all, BMS acted expeditiously and took action again immediately after the G2/21 decision, of which it could reasonably assume that it would result in an amendment of the preliminary relief court's assessment.

Violation of the closed system of legal remedies?

6.62 Sandoz furthermore objected to the grounds for appeal BMS formulated in the second preliminary relief proceedings (paragraph 5.21-5.26 Statement of Appeal) against the findings of the preliminary relief court in paras. 6.12-6.16 of the judgment dated I0 May 2022, which according to Sandoz et al. are unrelated to the test formulated in G2/21. According to Sandoz, it is allegedly contrary to the closed system of legal remedies if the Court of Appeal - notwithstanding the fact that BMS did not lodge an appeal against the first judgment- would assess those grounds for appeal in these second preliminary relief proceedings. No decision needs to be rendered in respect of that objection. As follows from the findings above, the Court of Appeal arrives at a different outcome with regard to the patent's inventive step based on a different interpretation ofG2/2l than the one the preliminary relief court started from. The Judgment will be set aside for that reason alone. The grounds for appeal which Sandoz objects to are not addressed.

Conclusion and claims

6.63 The conclusion is that that BMS's appeal is successful. The Court of Appeal is of the preliminary opinion that there is no substantial chance that the court hearing the case on the merit will deem EP 415 invalid. The fact Sandoz et al.'s generic apixaban product falls under the SPC's scope of protection is not in dispute. Therefore, the preliminary relief court's ruling cannot be upheld, and the Court of Appeal will set aside the Judgment.

6.64 The claimed order to cease infringement will be allowed, as will the order to remove generic apixaban from the G-standard, or to have it removed. The penalty attached to a violation of these orders will be et at EUR 100,000 per day, with part of a day counting as a full day, or EUR 1,000 per product, such at BMS's discretion.

6.65 It has not been argued with sufficient substantiation that and why any unlawful conduct occurred. For that reason, the claim to that end will be rejected.

6.66 The claimed statement will be allowed as claimed, with the exception that the claimed information pertaining to the calculation of damages or the surrender of profits. It has not been substantiated why BMS has an urgent interest in obtaining this information. The deadline for providing the required information will be set after two weeks after service of this judgment. In the context of these preliminary relief proceedings, the Court of Appeal sees no reason for an opinion from a registered accountant, also taking into account the urgency required by BMS. The penalty to be attached to the order is deemed to be a sufficient incentive to comply fully and correctly with the order imposed.

6.67 The claimed recall of infringing products within seven days after service of this judgment will be allowed as well. This can prevent any further infringements, in which BMS has an urgent interest given the findings at paras. 6.51 and 6.52. ft has not been substantiated why this term is allegedly unreasonably short. The statement and recall naturally apply only to the defendants that have entered the market with generic apixaban.

6.68 The claimed rectification is rejected. BMS has insufficiently substantiated why it has an urgent interest in this rectification in addition to the orders to cease infringement and to have apixaban removed from the G-standard.

6.69 The Court of Appeal sees no reason to attach an obligation to provide security to a declaration of enforceability regardless of any appeal. The assertion that Sandoz et al. incurs a recovery risk if BMS ultimately proves to be the unsuccessful party has not been sufficiently substantiated.

Costs of the proceedings

6.70 The Court of Appeal orders Sandoz et al., as the unsuccessful party, to pay the costs of the appeal. These costs will be calculated based on 1019h DCCP. The parties have agreed that these costs amount to EUR 60,000. As the Court of Appeal understands it, these costs pertain to both proceedings jointly and include disbursements, a specification of which is lacking. As it has not been further specified who will bear which share of these costs, the Court of Appeal will jointly and severally order Sandoz et al. to pay BMS's costs of the proceedings in the amount of EUR 783.

7. Decision

The Court of Appeal:

sets aside the judgment and, in a new judgment:

7.1 orders each of the defendants, with immediate effect after service of this judgment to cease and desist any infringement of the SPC in the Netherlands, on pain of a penalty of EUR100.000 (in words: one hundred thousand euro) for each day, with part of a day counting as a full day, that the defendant in question fails to comply with the order in full or in part, or - at BMS's discretion - EUR 1,000 (in words: one thousand euro) for each infringing product with which the defendant in question fails to comply with the order in full or in part;

7.2 orders each of the defendants, with immediate effect after service of this judgment, to remove its generic apixaban products from the G-standard, or to have them removed, on pain of a penalty of EUR l 00,000 (in words: one hundred thousand euro) for each day, with part of a day counting as a full day, that the defendant in question fails to comply with the order in whole or in part;

7.3 orders each of the defendants, within two (2) weeks after service of this judgment, to provide a statement to the address of BMS's counsel with regard to:

7.3.1 the full names and addresses of all domestic and foreign customers to which the defendant in question supplied infringing products, or substantial parts thereof, with a specification of the quantity of products or substantial parts thereof supplied, and the date of delivery;

7.3.2 the full names and addresses of all domestic and foreign suppliers from whom the relevant defendant obtained the infringing products or substantial parts thereof, with, for each supplier, a specification of the number of products supplied and the date of delivery;

7.3.3 the number of all infringing products manufactured, distributed and/or kept in stock by the defendant in question;
all of this substantiated by means of the relevant supporting documents;

7.4 orders each of the defendants, within seven (7) days after service of this judgment, to take back all infringing products supplied by the defendant in question from all of its customers, not being end users, with a refund of the purchase price paid and reimbursement of the transport costs relating to their return;

7.5 orders each of the defendants to pay an immediately payable penalty of EUR 100,000 (in words: one hundred thousand euros) for each violation of the order, or - at BMS's discretion - for each day the defendant in question acts contrary to the order imposed at paras. 7.3 and 7.4;

7.6 jointly and severally orders the defendants to pay the costs of these appeal proceedings on the part of BMS, estimated at EUR 60,000 and EUR 783 in court fees, plus the subsequent costs, with the stipulation that, if these costs have not been paid within two weeks after service of this judgment, the defendants will owe statutory interest on this amount without further notice;

7.7 declares this judgment immediately enforceable regardless of any appeal;

7.8 dismisses all other or additional claims.

This judgment was rendered by R. Kalden, presiding justice, and justices M.Y. Bonneur and P.H. Blok and, in the absence of the presiding justice, was signed and pronounced in open court by the eldest Justice on 15 Augusts 2023 in the presence of the court clerk.