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Case No: HP-2014-000040
Case No: HP-2015-000012
Case No: HP-2015-000048
Case No: HP-2015-000062

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

The Rolls Building
7 Rolls Building
Fetter Lane
London EC4A 1NL

Date: 10/08/2016

Before :

THE HON. MR JUSTICE BIRSS

- -

Between:

ACTAVIS GROUP PTC EHF **(A company incorporated under the laws of the state of Iceland)**	**Claimant in HP-2014-000040**
- and -	
ACTAVIS UK LTD	**Fourth Party in HP-2014-000040**
ACTELION PHARMACEUTICALS LTD **(a company incorporated under the laws of the state of Switzerland)**	**Claimant in HP-2015-000012**
- and -	
ACTELION PHARMACEUTICALS UK LIMITED	**Fourth Party in HP-2015-000012**
(1) TEVA UK LIMITED **(2) TEVA PHARMACEUTICAL INDUSTRIES LIMITED** **(a company incorporated under the laws of Israel)**	**Claimants in HP-2015-000048**
- and -	
GENERICS (UK) LIMITED (TRADING AS MYLAN)	**Claimant in HP-2015-000062**
ICOS CORPORATION **(a company incorporated under the laws of the state of Washington, USA)**	**Defendant**
- and -	
ELI LILLY AND COMPANY **(a company incorporated under the laws of Indiana, USA)**	**Third Party**

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Adrian Speck QC, Isabel Jamal, Joe Delaney and Tim Austen (instructed by Bird & Bird LLP) appeared for Actavis and Actelion and (instructed by Taylor Wessing LLP) appeared for Generics (UK) (trading as Mylan) and (instructed by Pinsent Masons LLP) appeared for Teva.
Michael Tappin QC also appeared for Actelion

Andrew Waugh QC, Thomas Hinchliffe QC, Katherine Moggridge (instructed Simmons & Simmons LLP) appeared for the Defendant and Third Party.
Thomas Mitcheson QC also appeared for the Defendant and Third Party

Hearing dates: 15th - 17th, 20th - 24th, 29th, 30th June and 1st July

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Judgment Approved

Mr Justice Birss

Introduction

1. These action is concerned with patents relating to tadalafil. Tadalafil is the generic name for a product sold under the brand name CIALIS for male erectile dysfunction and under the brand name ADCIRCA for pulmonary

arterial hypertension. CIALIS is also sold for benign prostatic hyperplasia. The patents and exclusive licences are held by Lilly and ICOS. In these actions, the pharmaceutical companies Actavis, Actelion, Teva, and Generics (UK) (Mylan) are seeking to clear the way. The relevant SPC expires in November 2017. The commercial value of these proceedings is very high. Based on public IMS data, branded sales of CIALIS for 2014 in the United Kingdom come to about $99 million while sales of ADCIRCA were $1 million. The European sales amount to about $¾ billion annually and Lilly's accounts for 2014 showed a figure of $2.29 billion for global turnover of CIALIS.

2. Two patents are in issue. EP (UK) 1,173,181, entitled "Compositions comprising phosphodiesterase inhibitors for the treatment of sexual dysfunction", was filed on 26th April 2000 claiming priority from US 132036P filed on 30th April 1999. The 181 patent was granted on 15th October 2003. The form of the patent before the court is a B3 specification following centralised amendments made in the EPO on 25th March 2015. The 181 patent relates to dosing. The other patent in suit is EP (UK) 1,200,092 entitled "Beta-carboline drug products". It was filed on 1st August 2000 claiming priority from US 147048P filed on 3rd August 1999. The 092 patent was granted on 21st April 2004. The 092 patent relates to drug formulation.

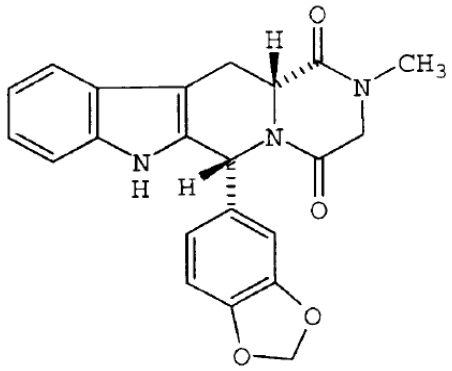
3. An important part of the context in this case relates to the famous drug VIAGRA. By the relevant priority dates (1999/2000), Pfizer had launched the compound sildenafil citrate under the brand name VIAGRA as a treatment for erectile dysfunction. It had attracted enormous public attention as well as attention in the pharmaceutical industry. VIAGRA was first launched in the USA after approval by the FDA in March 1998 so that by the earliest of the various possible priority dates it had been on sale for about a year. In fact at least in the industry it had attracted attention before launch. Sildenafil is an inhibitor of an enzyme known as phosphodiesterase 5 (PDE5). That enzyme acts in the corpus cavernosum tissue in the human penis and plays a role in maintaining erections. It is the inhibition of PDE5 which accounts for sildenafil's mode of action. Tadalafil is also an inhibitor of PDE5. Many of the issues involve considering the thinking of a person skilled in the art aware of sildenafil and considering tadalafil as another possible inhibitor of PDE5.

4. In the judgment I will refer to the two sides as "the claimants" and "Lilly". The claimants are Actavis, Actelion, Teva, and Generics (UK) (t/a Mylan)). In this judgment Lilly refers to both ICOS Corp. and Eli Lilly and Company. The proprietor of the patents is ICOS Corp. while Eli Lilly and Company holds an exclusive licence.

The issues

5. Claim 1 of 181 is in this form:

> A pharmaceutical unit dosage composition comprising 1 to 5 mg of a compound having the structural formula:



said unit dosage form suitable for oral administration up to a maximum total dose of 5 mg per day.

6. The structural formula represents tadalafil. The other relevant claims of 181 are set out in Annex 1.

7. There is a debate about claim construction concerning the reference to a maximum total dose per day. There are also issues on infringement which relates only to Actavis and Mylan. One is about whether a threat to infringe has been established and this applies to 181 and 092. The other is about the terms of the marketing authorisation(s) for the generic products. Most of the time at trial was taken up with issues concerned with validity. Recognising that Actelion does not challenge the validity of the 181 patent, I will still just refer to "the claimants" as a whole unless it is necessary to distinguish between them.

8. The claimants contend the relevant claims are not entitled to priority from the priority document. If priority is lost then further citations become relevant prior art (see below). The priority issue for 181 involves two points. First the claimants allege that tadalafil is not identified in the priority document or at least not identified sufficiently clearly nor in the correct context to support the claims of 181. This is mostly an argument about chemical nomenclature. Second the claimants allege that other features of the claims of 181 (relating to the maximum daily dose and/or amounts in dosage forms) are not supported in any event.

9. Lilly denies these allegations. It maintains that tadalafil is the compound disclosed in the priority document and the claims are entitled to priority.

10. The claimants take two added matter points against the 181 patent. They are similar to the second substantive priority issue but this time focussed on comparing the claims in force with the disclosure of the application as filed rather than with the priority document. The application as filed is said not to disclose dosage forms of from 1-5mg and not to disclose a maximum daily dose of 5mg. Lilly denies the patent includes added matter.

11. Four prior art citations are relied on: WO 97/03675 ("Daugan"), WO 01/08688 ("Anderson"), WO 00/53148 ("Stoner") and WO 01/08686 ("Oren"). Daugan

was published on 6th February 1997 and therefore is full prior art with respect to the 181 patent.

12. Anderson, Stoner and Oren were all published after the filing date for the 181 patent and therefore can never be relevant for obviousness. However they all designate both GB and EP(UK), amongst other states, and so may be relevant as novelty-only prior art under s2(3) of the Patents Act 1977 (Art 54(3) EPC). That will depend on dates and priority.

13. Anderson was filed on 1st August 2000 and claims priority from a US filing on 3rd August 1999. Therefore to the extent the 181 patent keeps its priority date Anderson is not relevant prior art at all. However if a claim of 181 loses priority, then to the extent any matter in Anderson is entitled to its own priority claim, it is citable for novelty against that claim. In fact Anderson is the PCT application which led to the 092 patent. No point is taken by Lilly that the matter in Anderson is not entitled to claim priority from Anderson's priority document.

14. Stoner was filed on 3rd March 2000 and so if 181 loses priority, the contents of the Stoner application are citable for novelty. Stoner claims priority from a US filing on 8th March 1999 which is earlier than the claimed priority date for the 181 patent, however in order for the claimants to argue that Stoner would be be citable under s2(3) even if 181 kept its priority date, it would be necessary to establish that the relevant matter in the Stoner application was entitled to priority from the relevant priority document. There was no suggestion that the matter relied on in the Stoner application might not be entitled to priority on substantive grounds but Lilly contends that the entitlement to make the priority claim in the application had not been established by the claimants.

15. As for Oren, its priority document was filed on 3rd August 1999 and the Oren application was filed on 26th April 2000. Thus if 181 loses priority and assuming Oren is entitled to its claimed priority, matter in Oren is citable against 181 as novelty-only art. Lilly did not dispute Oren's priority claim.

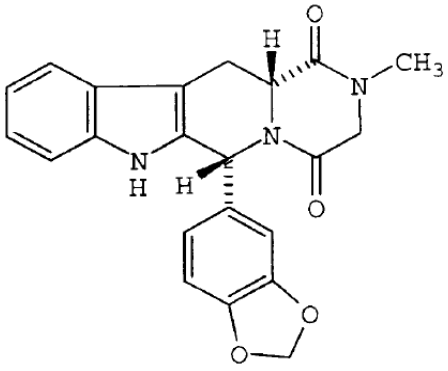
16. The claimants contend the claims lack novelty over Anderson, Stoner and Oren to the extent they are citable. They all disclose tadalafil, nevertheless up to trial Lilly had denied any of the claims lack novelty over any of these references. A general point related to some of the claims of 181 which are either in the Swiss form or EPC 2000 form in which the medical indication is erectile dysfunction. To deprive a claim of novelty the prior art must both disclose and enable the invention (***Synthon v SmithKline Beecham*** [2006] RPC 10). During trial Lilly admitted for the purposes of these proceedings that Anderson and Oren each include both a disclosure of the treatment of erectile dysfunction with tadalafil and an enabling disclosure of that as an efficacious treatment for erectile dysfunction. Consequently, Lilly also made clear that it would not defend the novelty over Anderson or Oren of any claim of 181 which lost priority. The position relating to Stoner is different because of an argument about whether Stoner is concerned only with combination therapies rather than monotherapy.

17. For inventive step the relevant prior art is just Daugan. The claimants contend all relevant claims of 181 are obvious in the light of Daugan, essentially because it would be obvious to carry out dose ranging studies in order to find the minimal effective dose for tadalafil and because a 5mg dose would be obvious in any event. Lilly does not agree. It contends that a dose of tadalafil as low as 5mg and the advantages it provides in terms of efficacy and low side effects were not obvious. Even if the skilled team embarked on a clinical research project into tadalafil starting from Daugan, they would have no reasonable prospect of success as to the outcome and no reasonable basis for thinking that a 5mg dose would be efficacious at all or would have the benefits it has. A skilled team which got as far as conducting phase II clinical trials of tadalafil would conduct studies with doses higher than those claimed.

18. The claimants also took an insufficiency point which was in the nature of a squeeze concerning the argument about disclosure and enablement of the relevant medical indication. Given Lilly's position on disclosure and enablement by Anderson and Oren, by closing the point was not live.

19. Claim 1 of the 092 patent is in this form:

> A free drug particulate form of a compound having a formula



> and pharmaceutically acceptable salts and solvates thereof in which the compound is present as solid particles not intimately embedded in a polymeric co-precipitate, wherein at least 90% of the particles have a particle size of less than about 40 microns.

20. The structural formula is the same one as in claim 1 of 181, i.e. tadalafil. The other relevant claims of 092 are set out in Annex 2.

21. There are two claim construction arguments. One relates to all claims and is concerned with whether the claim relates to a number average particle size distribution or a weight/volume average. There is also a point on claim 19 which is essentially the same as the 181 argument about maximum daily dose.

22. In addition to the threat to infringe question which applies to both 181 and 092, the only question of infringement about 092 which I have to decide

relates to claim 19 and is closely related to the infringement issues on 181 (albeit that claim refers to 20 mg/day rather than 5 mg/day). All other allegations of infringement of 092 by any of the claimants have been stayed on terms.

23. On priority two kinds of priority point are taken against 092 but only one type is live before me. The live issue is substantive priority (see below). The other issue is whether an entitlement to make the priority claim has been established (c.f. ***Edwards Lifesciences v Cook Biotech*** [2009] FSR 27) and as to that only Actelion maintain the objection. However Lilly and Actelion agreed that I do not need to make any findings or consider the issue because Actelion does not contest that the evidence establishes that Lilly has a good claim to entitlement to claim priority on equitable grounds and, based on authority binding at the High Court level, that would be enough. Actelion reserves the right to argue in a higher court that equitable entitlement is not sufficient and a legal as opposed to equitable claim has to be established. If that is the test there is a factual question to be decided but none of the written evidence was challenged in cross-examination and the parties were content to leave that for a higher court to consider if necessary.

24. As regards substantive priority, Lilly accepts that claims 8, 9, 16, 17 and 18 are not entitled to priority. That is because they include pharmacokinetic data (Cmax and AUC) which are not disclosed in the priority document. Lilly also accepts that insofar as claim 19 is dependent on any of those claims, it is not entitled to priority. It was common ground that for priority claim 19 can be treated as two distinct claims depending on its dependencies in the same way as I treated a claim in ***HTC v Gemalto*** [2013] EWHC 1876 (Pat), paragraph 121. As a distinct issue, the claimants contend claim 19 is not entitled to priority in any event, irrespective of claim dependency. That argument relates to the feature of claim 19 about dosing, which the claimants contend is not supported by the priority document. Lilly does not agree and so the issue is a live one.

25. A further point on priority is this. The claimants purport to admit for the purposes of these proceedings that the compound identified in the priority document for 092 is tadalafil. Lilly also contends that the compound is tadalafil. However subject to a trivial typographical error which the experts agree makes no difference, the name in this priority document is the same as appears in the priority document for the 181 patent. However, in the context of the 181 patent, the claimants argue that this name does not represent tadalafil but a different compound, and they called and cross-examined expert evidence on the point. In the end given my findings (below) this inconsistency does not matter.

26. The claimants contend claim 19 of 092 is invalid for added matter. This is about the "maximum daily dose" language in the claim and raises similar arguments to the case relating to 181.

27. On novelty, if priority is lost the claimants rely on Oren. Oren is not prior art against any claim in respect of which priority is maintained because Oren's priority document was filed on the same date as the priority document for 092

(3rd August 1999) and not earlier. On the other hand, for any claim in 092 which loses priority, Oren is novelty-only prior art at least because the Oren application was filed on 26th April 2000, which is before the 092 application.

28. The claimants contend all the claims of 092 which are not entitled to priority are anticipated by Oren. Lilly accepts that claims 1-7 and 10-15 lack novelty if they lose priority. For claims 8 and 9, which Lilly accepts are not entitled to priority, Lilly maintains that they are novel because a product with the relevant pharmacokinetics is not the inevitable result of what is disclosed by Oren.

29. For claims 16-19:

    i) Lilly accepts claims 16, 17 and 18 lose priority. They are Swiss form use claims dependent on claims 8 and 9. They stand or fall with claims 8 and 9.

    ii) The two notional claims encompassed by claim 19 are distinct. Insofar as claim 19 is dependent on claims 13-15 then, if priority is lost, Lilly accepts that notional claim lacks novelty. Insofar as claim 19 is dependent on claims 16-18 then, by virtue of the dependencies of those claims, claim 19 will include the features in claims 8-9 (for which the issue is the inevitability of the pharmacokinetics). That notional claim is not entitled to priority and it stands or falls with claims 8-9. If one of the two notional claims encompassed by claim 19 is valid and the other invalid, an amendment to the claim dependencies will be needed under s63.

30. For inventive step the prior art relied on by the claimants is again Daugan. All claims are said to be obvious over Daugan, essentially because it would be obvious to micronise the drug particles in order to ensure good bioavailability of tadalafil given its poor solubility. Lilly does not agree and maintains that while one might think of micronisation, it would be dismissed as an option not worth testing. Even if a micronized product was tested, the skilled person would not do so with a sufficient expectation that the test would work to reach the standard for obviousness.

31. The claimants take a number of points on insufficiency against 092. They are:

    i) Claims 8, 9, and 16 – 19 are too broad because they are limited by pharmacokinetics and not by particle size. There was also a squeeze on inevitable result.

    ii) The therapeutic indication claims 12 - 19 gave rise to two points but by closing only one was live. There had been a squeeze on disclosure/enablement as between Oren and 092 but this was dropped after Lilly accepted that the 092 claims (save for those dependent on claims 8-9) would lack novelty over Oren if they lose priority. The live argument is about claim 12. The claimants say it is either too broad or so ambiguous so as to be insufficient.

iii) The particle size feature in claim 1-7 raises an ambiguity insufficiency. The issue is about characterising particle size by volume or by number. Lilly contends the claim means volume. The claimants contend the claim covers either volume or number or both and if so is truly ambiguous.

The witnesses

32. I will mention the witnesses in the order they gave oral evidence.

33. The claimant's first expert witness was Dr Karl Gibson, a medicinal chemist. Lilly's first expert was Prof Timothy Donohoe. Dr Gibson and Prof Donohoe gave evidence about how the skilled person would understand chemical nomenclature and the particular chemical name which appears in the priority document for 181. Dr Gibson's opinion was that it was not tadalafil whereas Prof Donohoe's opinion was that it was.

34. Dr Gibson is the director and founder of Sandexis Medicinal Chemistry Limited, which provides medicinal and computational chemistry design services. Dr Gibson is CTO and also a founder of Ixchelsis Limited. Prior to these, he worked at Pfizer for just under 10 years as a medicinal chemist and research project leader. At the priority date, he held the position of senior research chemist at Merck Sharp & Dohme Research Laboratories, where he worked on the design and synthesis of novel target molecules for the treatment of diseases of the central nervous system.

35. Lilly submitted that Dr Gibson did not seek objectively to assist the court, that he sought more to argue the claimants' case and score points than to answer the questions put to him and that he was only willing to make assumptions in the claimants' favour. These are absurdly overblown submissions and I detected no support for them in his evidence. Dr Gibson was seeking at all times to explain his genuinely held views to me. Lilly made the point that Dr Gibson had not set out to find any other examples of the usage of the particular part of the chemical nomenclature which was in issue. He had never suggested that he had done such an exercise and explained orally that he had not done so because in his opinion the 006 document cross-referenced in the priority document supported the view he had reached. There is nothing in this as a reason to discount Dr Gibson's opinions. His evidence on Chemdraw was said to be "one-sided". That is not fair. I will deal with the Chemdraw issue on its merits. I reject Lilly's attack on Dr Gibson. It has no merit. Dr Gibson is a highly qualified expert doing his best to assist the court on a tricky and esoteric issue.

36. Prof Donohoe is a Professor of Chemistry at the University of Oxford, and served as Head of Organic Chemistry there between 2006 and 2011. He has held academic positions in organic chemistry and has run his own active research group since 1994. Prof Donohoe has also acted as a chemistry consultant for several pharmaceutical and chemical companies in the UK and the US, and is an author on over 160 research papers and reviews.

37. Rightly, the claimants made no personal criticism of Prof Donohoe. He gave his evidence fairly. The claimants submitted Prof Donohoe was far more skilled than the person skilled in the art and that Dr Gibson was better placed to give evidence about the position of the *ordinary* skilled chemist (their emphasis). I do not agree. Dr Gibson was an experienced medicinal chemist and Prof Donohoe taught individuals who went on to work in that role. Both witnesses were able to assist the court in relation to the views of the skilled person.

38. The claimants then called Mr Gary Muirhead. Mr Muirhead is a consultant to the pharmaceutical industry and CEO, Director and a founder of Ixchelsis Limited, a men's health biotech start up spun out of Pfizer. Prior to this he worked for Pfizer for nearly 20 years in various roles, first as a Clinical Pharmacologist, where he was involved in the planning, execution, analysis and report of Phase I/IIa clinical pharmacology studies and the production of Early Clinical Development plans, detailing drug development strategy from Phase I through to Phase II, then as a Senior Director. He was then appointed as the Executive Director and Site Leader of the Clinical Research Operations Group from 2006 to 2009.

39. Lilly submitted that Mr Muirhead sought to assist the court subject to the following difficulty, that he was heavily imbued with Pfizer's experience over 20 years including with sildenafil and that this made it difficult, if not impossible, for him to separate his personal experience from that of the notional skilled person. Mr Muirhead did indeed have very substantial experience with sildenafil as a result of his work at Pfizer but I did not detect any difficulty in his being able to distinguish between a skilled person who did not have Pfizer's experience and his own. Mr Muirhead was a good witness.

40. Next Lilly called Dr Jay Saoud. Dr Saoud is a Pharmaceutical Product Development Executive with over 25 years of experience in clinical development, pharmacokinetics and statistical analysis in industry, academia and contract research organisations. Dr Saoud joined ICOS Corporation in 1996 as Director of Biometrics, and worked on the development team of tadalafil. In 2001, he joined Aventis (later Sanofi-Aventis) as the US Product Realization Head for Clinical Pharmacology and Pharmacokinetics.

41. Dr Saoud gave his evidence fairly and the claimants did not criticise him.

42. Next Lilly called Dr Gerald Brock. He is a clinical urologist. Dr Brock is a Professor of Urology at the University of Western Ontario and a practising clinical urologist. He has been involved in research in the field of erectile dysfunction since 1991, and has run his own active research team since 1993. He has been involved as an investigator in a number of clinical trials for erectile dysfunction treatments, including tadalafil, and has authored over 150 peer-reviewed publications, primarily in the field of male sexual dysfunction. Dr Brock is currently Vice-President of the Canadian Urology Association. Dr Brock has extensive clinical, academic and advising industry experience, on matters concerning treatments for erectile dysfunction.

43. The claimants submitted that Dr Brock had a "keen appreciation of the shape of the arguments advanced by both sides and what points Lilly sought to advance" and, while he did not deliberately overstep the mark, he misjudged or misunderstood the role of an expert, perceiving what he was doing was within the rules and helpful to Lilly. This is similar to the criticism Lilly made of Dr Gibson but more elegantly put. I agree that Dr Brock appreciated the clinical issues in this case and he could be combative but I did not detect in his oral evidence anything to give me cause to discount his opinions as anything other than his sincerely held views. The particular points the claimants make: about his views about what Glaxo did or didn't do, about motivation over Daugan, and the concept of a minimal effective dose are matters I have had in mind at the relevant points in preparing this judgment. The claimants also submitted that Dr Brock "needed to slip in" something about ranges of maximum doses in cross-examination about his Canadian evidence. I think Dr Brock did seek to make a point which arose from the difference between this case and the case in Canada, which indicated that he understood the cases differed but I do not regard this as a major matter. I reject the claimants criticisms of Dr Brock.

44. Mr Muirhead and Drs Saoud and Brock gave evidence about clinical development and pharmacokinetics. Mr Muirhead's view was that for a skilled person reading Daugan it was obvious to take tadalafil forward and into clinical trials. His opinion supported the claimants in relation to the 181 patent and claim 19 of the 092 patent. Drs Brock and Saoud's opinions were to the contrary. Dr Brock gave evidence from the perspective of a clinician (i.e. a doctor), rather than the perspective of a clinical pharmacologist like Mr Muirhead. Lilly submitted that a significant omission in the claimants' case is that they could have but did not call a clinician. They were in touch with a clinician who is experienced in this field, Dr Ian Eardley. Dr Saoud is a clinical pharmacokineticist. The claimants contended that Dr Saoud accepted a number of important aspects of their case.

45. In respect of the formulation of pharmaceutical compounds relevant to the 092 Patent, the claimants called Prof Graham Buckton. Prof Buckton retired in 2015. He is an Emeritus Professor of Pharmaceutics at the UCL School of Pharmacy, and was Head of the Pharmaceutics Department from 2001 to 2007. He has taught various aspects of pharmaceutics in these roles, and has taught on many external courses for industry.

46. Lilly submitted that Prof Buckton had a tendency to avoid answering the questions put and fence with the cross-examiner. Subject to a minor point which I will deal with in context about the colon, there is nothing in this. Prof Buckton gave his evidence fairly and properly. Lilly also submitted that the way Prof Buckton was instructed undermined his evidence since he formed his views in the abstract and without knowledge of the properties of tadalafil. Subject to a point about surfactants which I will deal with in context, I do not accept that the manner in which Prof Buckton formed his opinions has any bearing on the weight I should attach to them. Prof Buckton is an experienced expert witness and has given evidence in a number of patent cases. He understood his role and was seeking to explain the technical issues and his

reasons for his opinions. Finally, Lilly submitted that Prof Buckton's approach to obviousness was that a skilled person would try all possible approaches without any real thought to whether they had any prospect of being successful. That is an inaccurate caricature of his opinion, which I will address in context.

47. The final expert called was Prof Henderik Frijlink, called by Lilly. He is Professor and Chairman of Pharmaceutical Technology and Biopharmacy at the University of Groningen's Institute for Drug Exploration, in the Netherlands. Between 1992 and 1998, he was Head of Pharmaceutical Development in the Dosage Form Development Department at Solvay, and was responsible for the development of new dosage forms and drug manufacturing processes. Prof Frijlink's mother tongue is Dutch but he gave evidence fluently in English. At one point counsel suggested that there may have been a language problem. I do not agree. The difficulty was not due to any lack of comprehension of the nuances of English by the Professor nor an inability to speak English, it was a disagreement of substance.

48. The claimants did not criticise Prof Frijlink directly but they emphasised the differences between his evidence in the Netherlands and in this court and suggested that he had been "carefully managed" by Lilly. I do not agree that a witness in Prof Frijlink's position should necessarily have gone out of his way to address in a report prepared for this jurisdiction why a report on the same patent in a different jurisdiction was prepared on a different basis. Of course experts ought to be consistent but they have enough to do without adding an extra obligation to explain in one jurisdiction what is going on in another. An expert may choose to do that in their report but it is no criticism of Prof Frijlink that he did not.

49. Prof Buckton and Prof Frijlink gave evidence about the formulation of tadalafil which was directed to the 092 patent. Prof Buckton's opinion was that micronisation was an obvious approach in order to improve the bioavailability of tadalafil. This would produce particles within the claimed size ranges. Prof Frijlink's evidence was to the contrary. His opinion was that while micronisation was well known, it would be thought not to be a viable way forward for tadalafil.

50. Lilly also relied on factual evidence from the tadalafil development project. This was given in witness statements from Dr Saoud and Dr William Pullman, who is a co-inventor of the 181 patent. Dr Pullman was head of the Lilly clinic with responsibility for clinical pharmacologists and clinical pharmacokineticists. After Dr Saoud's cross-examination the claimants indicated that they did not wish to cross-examine Dr Pullman.

51. Lilly also relied on two witness statements from Ms Ana Suarez-Miles, Assitant General Patent Counsel at Lilly. Her first statement put in evidence about the generic marketing authorisations acquired by various claimants. This has a bearing on infringement. Her second statement relates to the argument about chemical names and a point about Chemical Abstracts. It was served under a Civil Evidence Act notice. Ms Suarez-Miles was not cross-examined.

52. Each of the witnesses who gave oral evidence in this action was seeking to help the court. I am grateful to all of them for the time and effort they put in in order to explain their views to me.

Technical background

53. The parties were able to agree a technical primer which explained the technical background to the case. The parties agreed that the contents of the technical primer formed part of the common general knowledge subject to exceptions shown in the text. The following summaries are based on the primer and relate to the most significant points necessary to understand the issues in this case. It is all part of the common general knowledge.

Erectile dysfunction

54. Erectile dysfunction (also called impotence) is a medical condition described as the inability of a man to obtain and maintain an erection sufficiently hard for vaginal penetration and sexual satisfaction. Erectile dysfunction is an extremely common medical condition believed to affect upwards of 50% of men aged 40-70. Erectile dysfunction is one form of sexual dysfunction, which can also include ejaculatory and desire issues. The cause may be physiological, psychological or both. Examples of factors that can lead to physiological erectile dysfunction include hypertension, smoking, diabetes, drugs (both prescription and recreational), hormonal disorders, neurological conditions, physical trauma (such as pelvic surgery), Peyronie's disease, dyslipidemia (abnormal lipid levels) and venous leakage. Psychological conditions such as depression, guilt, stress, anxiety and relational discord may also lead to erectile dysfunction. Often there are a multitude of factors at work, with psychological factors induced by physiological factors.

The role of phosphodiesterases in erectile dysfunction

55. The human penis contains tissue called the corpus cavernosa. Tumescence and de-tumescence are caused by changes in blood volume in the corpus cavernosa. The flow of blood into the penis is controlled by smooth muscle found in the corpus cavernosa and in the arterial vessel walls. Smooth muscle is also found in many parts of the body including the lungs, the vasculature, the gastrointestinal tract and the uterus. Relaxation of smooth muscle in the penis allows blood to flow into the corpus cavernosa which swell. That swelling causes compression of the vessels through which blood would flow out of the penis, causing the penis to be engorged with blood and rigid.

56. Smooth muscle relaxation leading to an erection results from a cascade or series of highly complex biochemical reactions within the body. A "first messenger" such as the neurotransmitter nitric oxide (NO) or other hormones may initiate the cascade when released. The first messenger enters the smooth muscle cell or interacts with receptors on the cell surface, triggering an intracellular reaction. Molecules known as "second messengers" mediate the consequent intracellular reactions. In smooth muscle, these second messengers include the cyclic nucleotides, cyclic adenosine-3',5'- monophosphate (cAMP) and cyclic guanosine-3',5'-monophosphate (cGMP).

57. Sexual stimulation causes the non-noradrenergic, non-cholinergic (NANC) nerves to release NO. NO is ubiquitous in the body, and is responsible for initiating and mediating a large number of physiological reactions. NO enters smooth muscle cells and binds to guanylate cyclase. This enzyme catalyses the conversion of guanosine triphosphate (GTP) into the second messenger cGMP. In turn, cGMP binds to and activates an enzyme in the smooth muscle called cGMP-specific protein kinase (PKG) that regulates the activity of other intracellular proteins. The result of such activation of PKG is the relaxation of the smooth muscle cell.

58. A class of enzymes known as cyclic nucleotide phosphodiesterases (PDEs) regulate the intracellular concentrations of the second messengers cGMP and cAMP. These PDEs catabolise the second messengers by converting both cGMP and cAMP from their cyclic forms into their linear forms, GMP (guanosine-5'-monophosphate) and AMP (adenosine-5'-monophosphate). GMP and AMP are not agonists of PKG and therefore the activity of the PDEs reduces the overall activation of PKG present in the smooth muscle cell. Thus, increases in intracellular levels of cGMP (through NO production) promote smooth muscle relaxation, while decreases in intracellular cGMP levels (through hydrolysis by PDEs) result in the smooth muscle returning to its ordinary contracted state.

59. There are many subtypes of PDEs, but the most prevalent PDE in the corpus cavernosum is phosphodiesterase-5 (PDE5). PDE5 specifically binds cGMP, and hydrolyses it to its non-cyclic form, GMP. The action of PDE5 therefore decreases intracellular cGMP levels and reduces smooth muscle relaxation, thereby restricting arterial blood flow into the corpus cavernosum and preventing penile tumescence.

60. Sildenafil is a PDE5 inhibitor. By inhibiting PDE5, sildenafil prevents it from hydrolysing cGMP to the inactive GMP. As a result, in states of stimulation, cGMP levels remain elevated which promotes smooth muscle relaxation. This results in greater arterial blood flow into the corpus cavernosum and compression of the emissary veins, ultimately leading to penile tumescence.

61. At 30th April 1999 at least six PDE families were known – PDE1 to PDE6. PDEs 1 and 2 acted on both cGMP and cAMP as substrates. PDE3 and PD 4 were specific for the substrate cAMP while PDE5 and PDE6 were specific for cGMP. PDE6 was known to exist in the retina.

Potency and selectivity

62. The potency of a drug is the amount required to produce a defined biological effect of given intensity. Potency can be measured as the concentration (EC_{50}) or dose (ED_{50}) of a drug required to produce 50% of the drug's maximal effect as depicted by a graded dose-response curve. Alternatively, in the context of a drug that inhibits the action of another substance, it can be expressed as the concentration (IC_{50}) of a drug required to inhibit a given biological process by half i.e. the *in vitro* concentration of that drug which is required for 50% inhibition. A higher potency drug will have a lower IC_{50} because less drug will be required to achieve the same effect.

63. The selectivity of a drug to its target is determined by measuring the ability of the drug to bind not only to its target but also to other closely related receptors/binding sites and may be calculated by comparing IC_{50} values for other binding sites to the IC_{50} for the target. A drug that is highly selective is desirable, as off-target and non-specific binding can give rise to unwanted side-effects.

Measurement of Erectile Function

64. The measurement and quantification of erectile function is important both in terms of diagnosis (including assessing the severity of ED) and treatment (providing a measure of efficacy of, and the patient's response to, that therapy). A number of techniques were known to measure erectile function as at 30 April 1999. One was the Rigiscan system which was employed in nocturnal penile tumescence testing as well as in the clinical setting to measure erectile response to visual stimuli. This had been used widely to investigate the effects of potential treatments of ED. Rigiscan continuously monitors penile circumference to measure tumescence and rigidity.

65. The International Index of Erectile Function (the "IIEF") was published in 1997 as an alternative to pre-existing diagnostic techniques, many of which were laboratory based. Instead, it employs a self-assessment system whereby patients rate their erectile function over a course of sexual encounters which occur in more natural settings, principally their own homes. This reduces the influence of other external factors and results in a more realistic situation in which to record erectile function. The self-assessment is accomplished by the patient answering a questionnaire consisting of 15 questions about their sexual history over the past four weeks. To each question the patients gives a score of 0 (a negative answer) to 5 (a positive answer). The IIEF questions are also divided into five separate domains, with scores obtainable for each domain of sexual function. One of the domains is erectile function (questions 1-5 and 15) with a possible maximum score of 30. For the purpose of assessing erectile dysfunction, the erectile function domain is key and in particular the answers to questions 3 and 4. Those questions and the possible answers are:

> IIEF Q3 When you attempted intercourse, how often were you able to penetrate (enter) your partner?
>
> IIEF Q4 During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
>
> 0 – Did not attempt intercourse
> 1 – Almost never or never
> 2 – A few times (less than half the time)
> 3 – Sometimes (about half the time)
> 4 – Most times (more than half the time)
> 5 – Almost always or always

66. Other tools also existed as well as the IIEF, such as the Global Assessment Question (GAQ), the Global Efficacy Question (GEQ), and the Sexual Encounter Profile (SEP).

Formulation

67. In general when using the oral administration route drug products may be presented in several forms including solid dosage forms, suspensions and solutions. Generally solid dosage forms involve the compression or encapsulation of a powder consisting of the active pharmaceutical ingredient (API) and added excipients. Excipients can include diluents (bulking agents or fillers), disintegrants (to cause the tablet to disintegrate in water), and surfactants (which reduce interfacial tension between the solid drug and the dissolution medium, increase wettability and aid dissolution). In the 092 case there is a point about surfactants.

Bioavailability

68. Bioavailability refers to the extent and rate at which a drug enters the systemic circulation. The bioavailability of a drug is determined by its physico-chemical properties and the form and route in which it is administered. Differences in bioavailability among formulations of a given drug can have clinically significant effects on its safety and efficacy.

69. The most common method of assessing drug bioavailability is by determining its pharmacokinetic profile, achieved by measuring the blood plasma concentration time-curves i.e. plotting the concentration of drug in the blood plasma against time following administration. The data are most often obtained by conducting single-dose bioavailability studies in healthy volunteers, where blood samples are taken and assayed for drug concentrations at specific times post administration.

70. Immediately prior to the first administration of an oral drug to a subject, the concentration of drug in the blood plasma will be zero. Once absorption of the drug has begun in the GI tract, drug concentrations in the plasma should rise. This increase will continue until the drug reaches its maximum concentration. At this peak concentration (or Cmax), the rate of absorption of the drug is equal to its rate of distribution and clearance. The time at which Cmax is reached is known as Tmax. At times beyond Tmax the rate of distribution and clearance of the drug from the systemic circulation begins to exceed the rate of absorption, meaning that drug concentration in the plasma starts to fall.

71. Bioavailability is usually assessed by determining the rate and the extent to which a drug is delivered from a pharmaceutical form into the circulation. The rate is determined by the Cmax and Tmax and the extent is indicated by the area under the plasma concentration-time curve extrapolated to infinity (AUC). The AUC is directly proportional to the total amount of unchanged drug that reaches the systemic circulation.

The 181 patent

The skilled person and the common general knowledge – 181

72. The person skilled in the art in relation to the 181 patent would be a team. The team would include a number of members. It would include a clinical pharmacologist with experience in pharmacokinetics and a clinician specialising in urology. There was a dispute about the relative significance of the clinician member of the team as compared to the clinical pharmacologist. Another way in which the same dispute manifested itself was an argument about who would lead the team in particular contexts. In the end I did not detect a dispute of principle between the experts. Essentially Mr Muirhead (a clinical pharmacologist) emphasised the importance of the clinical pharmacologist whereas Dr Brock (a clinician) emphasised the importance of the clinician.

73. My findings are as follows. Both kinds of skilled person would be important members of the team, bringing their different perspectives to bear. Their relative significance varies depending on the particular issue which the team has to consider. Quantification of doses and the dose response was a matter primarily for the clinical pharmacologist, working with all members of the team, including the clinician. Since the clinician is the only team member with experience of treating patients, they will have a particular importance when assessing the clinical significance of an effect – whether it is a desired effect or a side effect. With an eye on questions which will arise in due course, I find that the clinical pharmacologist will take the lead in selecting doses to be tried in the dose ranging study or studies which would follow a successful Phase IIa study, albeit with input from the clinician. However it is the clinician who would take the lead, albeit with input from the clinical pharmacologist, in considering the likely clinical significance of possible effects.

74. There was no dispute about the legal test for common general knowledge. I will not rehearse it. In this section when I say "known" I mean part of the common general knowledge.

75. In addition to the background matters set out above, the following topics need to be considered in order to identify relevant common general knowledge:

    i) The phases of clinical research

    ii) Minimal effective dose

    iii) Sildenafil

    iv) Second in class

    v) Chronic dosing

The phases of clinical research

76. Clinical research into new medicines follows a standard path consisting of a series of phases. A chemical compound is identified as a putative new drug in

in vitro studies based on a rationale that the effect of the compound may have clinical relevance. So, for example, the notion that a selective PDE5 inhibitor may treat erectile dysfunction may make it rational to identify selective PDE5 inhibitors by *in vitro* testing. Once a compound has been identified it is tested in pre-clinical animal studies. As well as toxicity, as best it can the team will look for any efficacy information (for example in an animal model of the disease) and pharmacokinetic information. Assuming the decision is positive, the first tests in humans are Phase I studies in healthy volunteers. These test safety rather than efficacy since the patients are healthy. The tests provide pharmacokinetic information and allow an assessment of bioavailability. Assuming the decision after Phase I is positive the next step is Phase II. These consist of studies in patients with the disease and consider efficacy as well as safety and tolerability. The term tolerability has two slightly different meanings. Used loosely the term just refers to the general severity of side effects. The term can also refer more precisely to the balance between efficacy and side effects. So even if a relatively high but safe dose is required for efficacy and that dose produces some side effects, if those side effects amount to an acceptable trade-off for the positive effect of the drug, the dose is tolerable.

77. Phase II studies generally consist of a Phase IIa "go no-go" study. "Go no-go" refers to the decisive nature of the test. Phase IIa studies can also be called Proof of Principle or Proof of Concept studies. There may be a shade of difference in meaning between these two but it does not matter. There was a modest dispute about what sort of dose or doses would be chosen for a Phase IIa study. I find that a Phase IIa study will generally be done at one dose, selected to be high enough to give the drug the best chance of showing a positive effect on the disease albeit not too high to risk serious side effects.

78. Assuming the "go no-go" decision is positive, a dose ranging Phase IIb study will then be conducted. This involves testing a range of doses. The range to be tested is chosen to show an effect of dose. In other words the idea is that the highest dose will show a larger clinical effect than the smallest dose. Phase IIb studies are conducted in a larger number of patients than Phase IIa. A small point on statistics came and went in the trial. Although adding more dose arms to a study does have an effect on the ability of a given study to detect statistical significance of a given dose, that only matters if one is considering pairwise comparisons (placebo vs a single dose). In dose ranging studies a known way of carrying them out is to test the statistical significance of the dose response itself against placebo. Doing it that way does not create the same problem.

79. A second point on statistics is this. There is a key difference between clinical significance and statistical significance. The two are distinct. An effect may be clinically insignificant in the sense that the effect is too small to be of any real benefit to patients and yet it may be statistically significant in the sense that the statistics of the study allow one to conclude that the effect really is caused by the drug.

80. Assuming the decision after Phase II is positive, the next phase is Phase III. These are large scale clinical trials in order to generate data to support the

application for marketing approval from the regulators such as the FDA in the USA and the EMEA in Europe. Phase IV studies occur after regulatory approval.

81. This path would be well known to the skilled team as an idealised version of what happens. The team would also be well aware of the complexity and cost of these steps. Carrying out clinical research is not a mechanical process. Moving along the path involves larger and larger studies in increasing numbers of patients and very significant cost, time and trouble. The skilled team would be acutely aware of this and would also know that real projects can involve more steps and more tests.

Minimum effective dose

82. A major dispute was about minimum effective dose but the evidence was clear. The concept of a minimum (or minimal) effective dose was part of the common general knowledge of the skilled team, particularly the clinical pharmacologist but also the clinician. It is the smallest dose of a drug which will cause a clinically relevant effect. The concept was referred to in numerous textbooks and all four of Mr Muirhead, Dr Saoud, Dr Brock and Dr Pullman were familiar with it. Dr Pullman was not cross-examined but he had referred to it in his Canadian evidence which was put to Dr Saoud.

83. The skilled team were also aware that pharmaceutical regulators could ask a developer to identify it but that cannot be taken too far. The evidence did not establish that it would always be required for every project. Nevertheless the fact that regulators could be interested in it was part of the common general knowledge.

84. There was a point about whether the minimum effective dose was simply the lowest effective dose in a tested dose range. In a range of doses tested in a dose ranging study, it is possible to refer to the lowest effective one in the test as the minimum effective dose in that test. Depending on context that could be what someone is talking about but it is not normal usage and it is not what the term means.

85. It was not established that the skilled team would always seek to pin down what the minimum effective dose for a given drug actually was. Knowing that a minimum effective dose is somewhere in a range can be sufficient (that is what happened with sildenafil). The concept is one which the skilled team will have in mind but, like so much of pharmaceutical development, it depends on value judgments made in context. The primary task of the skilled team is to make safe, tolerable and effective medicines. A relevant issue in the context of erectile dysfunction is that there was no agreed definition of a minimum clinically relevant effect at the priority date. I will return to this in context below.

Sildenafil

86. The common general knowledge relating to sildenafil was important. By the priority date sildenafil was already very successful and extremely well known

by those in the art. It was already a blockbuster. The market for oral erectile dysfunction medication was large and very attractive.

87. Sildenafil was known to be administered on demand. Its pharmacokinetics meant that its onset of action was about 1 hour on average but could be delayed if taken with food. This lack of spontaneity was a known drawback of sildenafil. Sildenafil's half-life is about 4 hours which means that there would be no significant accumulation if taken once daily.

88. The mode of action of sildenafil as a PDE5 inhibitor was known to the skilled team. What was also known was that while sildenafil was selective for PDE5 its potency for PDE6 was only 10 times less than for PDE5. Two reported values for the IC_{50} of sildenafil against PDE5 were known, of 3 nM and 3.9 nM. Sildenafil's effect on PDE6 was associated with known visual side effects of sildenafil. The drug was also associated with side effects including flushing, headache, dyspepsia and others. They were normally mild and transient. Sildenafil was and still is contra-indicated for concomitant administration with nitrates.

89. Aside from vision, the side effects I have mentioned were thought to be related to its mode of action as a PDE5 inhibitor because PDE5 was known to exist in a number of peripheral sites in the body such as visceral and vascular smooth muscle. The contra-interaction with nitrates can be explained by reference to the nitric oxide pathway. Nitroglycerin is a cardiac medicine which produces a rapid release of NO and causes vasodilation by increasing cGMP levels. Exposure to high levels of NO and in conjunction with PDE5 inhibition can cause hypotension (a fall in blood pressure).

90. There was a dispute about exactly what the skilled team would think about the dosing of sildenafil. Essentially Lilly sought to emphasise higher doses while the claimants sought to emphasise lower does. In my judgment the common general knowledge was as follows. Sildenafil was known to be marketed at doses of 25mg, 50mg and 100mg and it was known that broadly efficacy increased with dose and so did side effects. Those three doses are the doses a skilled team would focus on albeit, as the claimants established, it was also known that a 10mg dose of sildenafil had been investigated in trials and shown to be efficacious. A landmark paper was Goldstein (1998) published in the New England Journal of Medicine. Lilly, supported by Dr Brock, emphasised a particular aspect of Goldstein, in that in one dose escalation study patients could change to a higher or lower dose over time. At the end of the study only 2% were on the 25mg dose while 74% had selected the 100mg dose. In argument counsel for Lilly placed undue emphasis on this result. The skilled team would not think that it meant that a 25 mg dose of sildenafil was not effective or worthwhile either clinically or commercially. The correct way of characterising the thinking of the skilled team is that they would not simply focus on a 25mg sildenafil dose. They would have all three doses well in mind and would know that the most clinically effective and popular doses were the higher ones.

Second in class

91. Sildenafil was a first in class drug. Its success validates the rationale for trying to treat erectile dysfunction using an oral drug which is a PDE5 inhibitor. Another PDE5 inhibitor for erectile dysfunction would be known as second in class. The general idea of first and second in class drugs was common general knowledge.

92. Dr Brock described the impact of sildenafil on the skilled team as "huge". What he was getting at was that it would be a helpful comparator. Mr Muirhead said that a clinical pharmacologist has an expectation that a second in class drug will also be efficacious given the efficacy of a first in class product. Dr Saoud agreed that with a second in class drug the skilled person would have an enhanced expectation of efficacy. None of these witnesses was suggesting that success was inevitable. As Dr Brock put it, while they would have a higher level of confidence in being able to find an efficacious dose of a second in class drug, it would not be a "slam dunk".

Chronic dosing

93. The claimants submitted that the benefits of chronic daily dosing of a drug for erectile dysfunction were part of the common general knowledge. This is one of those debates which shades between inventive step and common general knowledge. The skilled team would know that some drugs for some conditions are taken on demand while others are taken chronically. For chronic use, drugs are often taken daily. The skilled team would also know that side effects which may be acceptable with an on demand drug because they are transient may not be acceptable with chronic administration.

94. The skilled team would know that sildenafil was used on demand. They would also know that its pharmacokinetics were consistent with that.

95. Mr Muirhead explained that Pfizer had not created a daily dose for sildenafil because of its short half-life but while that may be indicative of the thinking of a skilled team in a given situation, Pfizer's actual thinking was not part of the common general knowledge.

96. Whether a skilled team given the Daugan prior art would think about chronic daily dosing, and if so what then, are matters best dealt with in relation to obviousness. In my judgment without a prompt, the idea of investigating chronic dosing of a drug for treating erectile dysfunction was not part of the common general knowledge.

Stereochemistry

97. Stereochemistry is concerned with the shape of chemical molecules considered in all three dimensions. The stereochemistry of a compound will often dictate how it behaves in biological systems and can be critical in drug design. A relevant concept in stereochemistry is a stereoisomer. Isomers are different compounds with the same molecular formula. Structural isomers have the same number and type of atoms but they are attached to each other in different ways. Stereoisomers have the same molecular structure and the same arrangement of atoms but differ in the spatial configuration of the atoms.

Stereoisomers are "locked" relative to one another and the molecules cannot be "twisted" from one configuration to the other.

98. A carbon atom has four bonds. If it has four different groups or atoms attached to it, then that molecule can exist in two non-superimposable mirror image forms called enantiomers. They are stereoisomers. The carbon in that case is known as a chiral centre.

The 181 patent specification

99. Paragraph [0002] of the description explains that the invention relates to a highly selective and potent inhibitor of PDE5 for the treatment of sexual dysfunction with minimisation or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes.

100. The background section from paragraphs [0003] to [0006] explains the rationale for treating sexual dysfunction with a PDE5 inhibitor, discusses the commercial success of sildenafil, mentions sildenafil's only 10-fold selectivity for PDE6 and the possible effect on vision, and discusses the contraindication with organic nitrates.

101. Paragraph [0007] acknowledges the Daugan reference as prior art.

102. Paragraph [0008] states that the inventors have discovered that one "such compound" (i.e. a compound of the class disclosed in Daugan) "can be administered in a unit dose that provides an effective treatment without the side effects associated with…sildenafil". This compound is referred to in the patent as Compound (I) and is now called tadalafil. The paragraph ends with the statement that "Prior to the present invention such side effects were considered to be inherent to the inhibition of PDE5".

103. Paragraphs [0009] and [0010] are as follows:

> "[0009] Significantly, applicants' clinical studies also reveal that an effective product having a reduced tendency to cause flushing in susceptible individuals can be provided. Most unexpectedly, the product also can be administered with clinically insignificant side effects associated with the combined effects of a PDE5 inhibitor and an organic nitrate. Thus, the contraindication once believed necessary for a product containing a PDE5 inhibitor is unnecessary when Compound (I) is administered as a unit dose of about 1 to about 20 mg, as disclosed herein. Thus, the present invention discloses an effective therapy for sexual dysfunction in individuals who previously were untreatable or suffered from unacceptable side effects, including individuals having cardiovascular disease, such as in individuals requiring nitrate therapy, having suffered a myocardial infarction more than three months before the onset of sexual dysfunction therapy, and

> suffering from class 1 congestive heart failure, or individuals suffering from vision abnormalities.
>
> [0010] The present invention relates to Compound (I) in a unit dosage form. That is, the present invention relates to a pharmaceutical unit dosage form suitable for oral administration comprising about 1 to about 5mg Compound (I)."

104. These paragraphs emphasise the point made in paragraph [0008] that the compound can provide efficacy with a reduction in side effects as compared to sildenafil. The upper level for the tadalafil dose in paragraph [0009] is 20 mg whereas the claims are limited to a maximum of 5mg per day.

105. In the next section entitled Summary of the Invention, the patent essentially describes what is claimed in claim 1. The section, also describes erectile dysfunction specifically.

106. The Detailed Description section starts at paragraph [0016] with various definitions. Paragraph [0024] refers to a dosage form being packaged as an article of manufacture comprising a package insert, a container and a dosage form. Normally this sort of description in a patent for a pharmaceutical product would not excite any interest but given one of the issues on infringement it is worth drawing attention to. The package insert is a leaflet which is put inside the box (container) along with the pills (dosage forms). Paragraph [0025] states that the package insert provides a description of how to administer a pharmaceutical product, along with safety and efficacy data required to allow the physician, pharmacist and patient to make an informed decision regarding the use of the product. The paragraph also states that the package insert will provide instructions to administer one or more about 1 to 5mg unit dosage forms as needed, up to a maximum total dose of 5mg per day. Paragraph [0027] refers to what the package insert says about side effects.

107. The next significant paragraphs start at [0031] in which the patent states that the invention is based on experiments and clinical trials and the "unexpected observations that side effects previously believed to be indicative of PDE5 inhibition can be reduced to clinically insignificant levels by the selection of a compound and unit dose" and that this enabled the development of a unit dosage form that incorporates Compound (I) in about 1 to about 5 mg per unit dosage forms that, when orally administered, minimises undesirable side effects previously believed unavoidable. These side effects include facial flushing, vision abnormalities, and a significant decrease in blood pressure, when Compound (I) is administered alone or in combination with organic nitrates.

108. Paragraph [0034] reports the IC_{50} data for tadalafil: 2.5 nM vs PDE5, 3400 nM vs PDE6 giving a ratio of PDE6/PDE5 of 1360. The IC_{50} value for PDE 1c is also reported along with the PDE1c/PDE5 ratio.

109. The examples start at paragraph [0059] following a description of various preparatory steps and assays. Examples 1 to 4 give examples of formulations

and their method of manufacture, containing dosage forms with 1mg, 2.5mg, 5mg and 10mg of tadalafil in various forms. Example 5 describes a clinical study which evaluated the haemodynamic effects of concomitant administration of tadalafil and short-acting nitrates on healthy male volunteers. The patients were administered sublingual nitroglycerin, along with a daily dose of placebo or 10mg of tadalafil for seven days. The study found that there was "minimal, if any, effect on mean systolic blood pressure" and that the most common side effects recorded were headache, dyspepsia and back-pain.

110. Example 6 describes two studies, stating that both daily dosing and on demand therapy with tadalafil were used. It reports that doses from 5mg to 20mg were found to be efficacious and demonstrated "less than 1% flushing" and no reports of vision abnormalities. It states that a 10 mg dose of tadalafil was fully efficacious and demonstrated minimal side effects and that it "significantly improved the percentage of successful intercourse attempts, including the ability to attain and maintain an erection in both "on demand" and daily dosing regimens".

111. Example 7 describes a clinical study in which two hundred and twelve men with mild to severe erectile dysfunction received on demand therapy with tadalafil, at doses of 2mg, 5mg, 10mg, 25mg and placebo. The doses were administered no more than once per twenty four hours. The primary efficacy variables were recorded by IIEF questions 3 and 4, and the secondary efficacy variables were scores across the IIEF domains and responses to the SEP and GAQ. Statistically significant increases over placebo were recorded at all doses for IIEF Question 3 (ability to penetrate). For Question 4 (ability to maintain an erection), only the 5mg, 10mg and 25mg doses provided statistically significant increases over placebo. The example also notes that the most commonly recorded side effects were headache, dyspepsia and back-pain and states that the "*incidence of treatment-emergent adverse events appeared related to dose*". Example 7 concludes that the results, when combined with the secondary efficacy variables, show that all four tested doses exhibit significant improvement relative to placebo.

112. The table at paragraph [0085] shows combined results from clinical studies. Presumably the studies are the ones in the patent although that is not explicit. The table summarises the changes from baseline in erectile dysfunction domain scores and shows an increase between 2mg, 5mg and 10mg, flattening off between 25mg and 100mg. The table is:

IIEF ERECTILE FUNCTION DOMAIN (Change from Baseline)			
Unit Dose of Compound (l)	**n**	**Mean ± SD**	**p**
placebo	131	0.8 ± 5.3	
2 mg	75	3.9 ± 6.1	<.001
5 mg	79	6.6 ± 7.1	<.001
10 mg	135	7.9 ± 6.7	<.001
25 mg	132	9.4 ± 7.0	<.001
50 mg	52	9.8 ± 5.5	<.001
100 mg	49	8.4 ± 6.1	<.001
n is number of subjects, SD is standard deviation.			

113. A second table at paragraph [0086] summarises the percentage of treatment-emergent adverse effects recorded across the dose range. This table is:

Treatment-Emergent Adverse Events (%)							
Unit Dose of Compound (l) (mg)							
Event	**Placebo**	**2**	**5**	**10**	**25**	**50**	**100**
Headache	10	12	10	23	29	34	46
Dyspepsia	6	3	14	13	19	20	25
Back Pain	5	3	3	15	18	24	22
Myalgia	3	0	3	9	16	20	29
Rhinitis	3	7	3	4	4	0	2
Conjunctivitis	1	0	1	1	0	2	5
Eyelid Edema	0	0	0	1	1	2	3
Flushing	0	0	0	<1	0	3	7
Vision Abnormalities	0	0	0	0	0	0	0

114. This table shows similar levels of adverse effects at the 2mg and 5mg doses as compared to placebo, for headache, back pain, myalgia and flushing. Dr Brock drew a contrast between the level of side effects which are tolerable to patients concerned with erectile dysfunction as opposed to some other conditions, given that ED is a quality of life issue rather than, for instance, a life threatening disease. His view was that side effects such as headache, backache, myalgia and flushing have a significant impact on patient tolerability in ED, and therefore the lower incidence of these effects at the claimed doses of 2mg and 5mg would be seen as a real advantage of the lower dose. I accept that evidence.

115. The description ends at paragraph [0087] with a statement that emphasises the invention (in terms of claim 1 – i.e. a maximum daily dose of 5mg) as being effective to treat erectile dysfunction and minimising or eliminating the occurrence of adverse side effects.

116. The claimants pointed out that in fact the regulatory approvals for tadalafil include a contraindication for nitrates. The fact this is required by the regulators does not negate the teaching of the patent that the tendency of PDE associated side effects, including an interaction with nitrates but also facial flushing and vision abnormalities, are reduced with tadalafil. I find that at the doses claimed tadalafil is not only an effective treatment for erectile dysfunction but does have a reduced tendency to side effects associated with its mode of action as a PDE inhibitor as compared to sildenafil.

Claim construction - 181

117. Lord Hoffmann summarised the law on claim construction in ***Kirin-Amgen*** [2005] R.P.C. 9. The question is always what the skilled person would understand the patentee to be using the words to mean. Jacob LJ summarised the effects of the judgment in ***Kirin-Amgen*** and gave guidance on the principles to be applied in ***Virgin Atlantic Airways v. Premium Aircraft Interiors*** [2010] R.P.C. 8 at paragraph 5.

118. The only real dispute was about the meaning of words in claim 1 which refer to a maximum dose. Before dealing with that it is convenient to deal with issues which were not controversial between the parties.

119. Claim 1 claims a pharmaceutical dosage form composition with various characteristics. It is therefore a claim to a product such as a tablet, liquid or capsule. I will refer to it as a tablet without limitation. The individual tablet must comprise 1 to 5 mg of tadalafil. It must be suitable for oral administration up to a maximum total dose of 5 mg per day. The requirement of suitability for oral administration causes no difficulty. It is not clear what effect on the scope of the claim would be understood by the skilled reader to be intended by the inventor by the requirement to be "suitable for" administration up to a maximum daily dose. "Suitable for" would be understood as conventional language almost always used in patents to refer to an objective characteristic (cf ***Virgin*** paragraph 15). The distinction is with something which is "intended for" a particular use. Notable by its absence is any reference in claim 1 to the clinical indication. That comes in claims 6 – 9 while claim 10 is a use claim written in the conventional Swiss form. Given the later claims neither side really focussed on this point about the scope of claim 1. In my judgment in claim 1 the words "up to a maximum total dose of 5 mg per day" have no effect on the scope of the claim. The claim is simply to a tadalafil tablet (or other dosage form) suitable to be given orally containing 1 to 5 mg of the drug. Such a tablet is inherently *suitable for* administration up to a maximum total dose of 5 mg per day. Whether a doctor prescribes its use in that way is not relevant. Such a tablet could be administered in that way. The alternative would be to say that such a tablet can never be suitable for that sort of administration unless one knows how it has been prescribed. But that is unreal and since the patent includes claims 7-9 and claim 10, the skilled reader would see no reason to interpret claim 1 that way.

120. Claims 2 and 3 limit the amount of drug in the tablet to 2.5 mg or 5mg respectively. The next important claim is claim 7 which together with claims 1 and 6 makes an EPC 2000 purpose limited product claim. Now the tablet

must be for use in treating sexual dysfunction. Male erectile dysfunction is referred to in claim 8 as a sub-set of sexual dysfunction but nothing turns on that. As an EPC 2000 claim, the treatment of sexual dysfunction is a functional technical feature of that claim. Whatever they mean (see below) the inclusion of the words "up to a maximum total dose of 5 mg per day" now makes sense. Read as a whole, for this claim the attainment of the effect – treatment of sexual dysfunction – must be something which does occur up to a maximum total dose of 5mg per day.

121. Claim 10 has a scope which more or less corresponds to claim 7 albeit in Swiss form rather than EPC 2000 form. The claim requires use of a "unit dose" (again e.g. a tablet) containing 1-5mg, the functional technical feature is the treatment of sexual dysfunction and this effect must be achieved with administration up to a maximum daily tadalafil dose of 5mg. Claim 10 is not limited to oral administration but nothing turns on that. Claims 12 and 13 limit the amount of drug in the same way as claims 2 and 3.

122. Importantly (and Lilly did not suggest otherwise although at times its argument seemed to stray in that direction) these claims are not limited to chronic administration but encompass on demand use of tadalafil as well.

Up to a maximum total dose of 5 mg per day

123. This issue caused real confusion at trial. The claimants submitted that the claim must be referring to a maximum dose approved for the patient population and therefore exclude the case in which a doctor might prescribe tadalafil to some patients at 5mg and others at 20mg. In that example the claimants submitted the *maximum* daily dose would be 20 mg rather than 5 mg and argued that to say that the prescription of the 5mg dose was within the scope of the claim would give the word maximum no meaning. In oral submissions counsel for Lilly accepted that the claim referred to a population but in the course of argument it became less clear to me what Lilly's case was on this.

124. As with some problems of construction it is best understood with an eye on infringement (recognising that the true construction of the claims takes place without looking at the alleged infringement). Lilly's case was that if one looked at the Summary of Product Characteristics (SmPC) for a tadalafil 5 mg tablet, the fact that dosing of 5mg per day for chronic once daily dosing is approved (see the Actavis 5mg SmPC paragraph 4.2) means that the claim is infringed. So far so good until one saw that the same paragraph in the SmPC also contemplates higher doses such as 10mg and 20 mg for on demand use, with a maximum dose frequency of once per day. So the 5 mg tablets are approved for on demand prescription as long as the maximum dose is no more than 10 or 20 mg per day.

125. I confess I did not understand Lilly's case on this. It seemed at one stage to be trying to focus only on the parts of the SmPC concerned with chronic administration for which the maximum approved dose is indeed 5mg per day. However that will not do because the claim is not limited to chronic dosing. The problem was not helped by the fact that Lilly treated infringement as a

minor matter, as if all that had to be shown was that the generic marketing authorisations for the Actavis and Mylan products would follow the CIALIS label (which one would expect in any event). The word "label" in Lilly's opening and closing skeletons being a reference to the SmPC. The submission was that if the label includes "a recommendation of dosing up to 5mg once a day" then the claim would be satisfied. This did not face up to the problem that the label also includes a recommendation of dosing up to 10mg and 20 mg once a day, which Lilly must have been well aware of since it is based on the CIALIS label.

126. In response Lilly sought to rely on the Actavis and Mylan patient information leaflets (PILs) (which go in the box of 5mg or 2.5 mg tablets). The highest dose mentioned in these PILs is 5mg per day. Consistent with this the leaflet seems to be focussed only on chronic daily dosing of tadalafil for which 5 mg per day is the maximum recommended in the SmPCs above. I gave leave to allow Lilly to put them before the court even though they came after the evidence. It did not prejudice the claimants since neither side called any witnesses to address these issues. The court has been left to make what it can of the documents. The claimants' submission was they were the wrong sort of documents since they were aimed at the patient rather than the doctor. To infringe a use claim or EPC 2000 claim the claimants submitted the focus had to be on what a doctor prescribes and the information provided to the doctor.

127. The ***Pregabalin*** litigation (see the ***Warner Lambert*** cases such as [2015] EWCA Civ 556 and [2015] EWHC 2548 (Pat)) was mentioned but while those decisions are clearly relevant to the general question of construction and infringement of Swiss style and EPC 2000 claims, neither side submitted they shed any light on this issue.

128. After the closing Lilly's counsel then sent an email purporting just to give the court a reference to a passage from ***Merck v Actavis*** [2008] EWCA Civ 444 at paragraph 10 but in fact containing further submissions on this issue. Counsel had submitted in argument that Jacob LJ had held that the PIL was the relevant document and he would get the reference (Day 11/1783) but the email shows that the relevant passage from the judgment does not help. There is no dispute that the problem of infringement of use claims may be more theoretical than real in medical cases owing to the existence of documents of this general type because they set out detailed instructions and information about uses and dosage, as paragraph 10 of ***Merck v Actavis*** explains. However in that passage the Court of Appeal was not distinguishing between an SmPC and a PIL.

129. The further submissions in the email were:

> "1. As regards the significance of the *Warner-Lambert* (pregabalin) case, the facts in that case were that the infringing directions were left out (ie carved out) of the label and the alleged infringing use for pain was 'off-label'. (ie the patented use pregabalin for pain was excluded from the label).

> 2. In the current case, the on-label use infringes where the direction on the 2.5mg and 5mg tablet Patient Information Leaflets is to use of the 2.5mg and 5 mg tablets up to a maximum daily dose of 5mg.
>
> 3. The use of the 2.5mg and 5mg tablets at higher doses (greater than 5mg) for daily use is not indicated on the PILs nor is their use at lower doses (5mg or less) for on demand use though even if the latter were used, this would still take advantage of the fact that at the doses of 5mg and lower there is efficacy to treat but with minimal side effects akin to placebo."
>
> (numbering added)

130. Point 1 does not advance the issue. Point 2 suggests that the PIL contains a direction about how the tablet is to be used. It is true that there are directions in the PIL but absent evidence I do not accept it is as simple as that. The issue may depend on whether this is a prescription only medicine or whether this is also available from pharmacists over-the-counter (OTC). No evidence was called about that. For a prescription medicine the patient is directed by the doctor how to take the drug and so the PIL is not really what tells the patient what to do. What information informs the doctor? Absent evidence I would expect it to be more likely to be the SmPC rather than the PIL. Point 3 is an accurate characterisation of the information on the PIL, leaving aside the rhetoric in the last clause.

131. To support its reliance on the PIL, Lilly also referred in argument to the fact that the patent discusses the "package insert", which is another name for the PIL. This concerned me but in the end I do not think it helps. The Swiss style and EPC 2000 claims are in conventional form (***Virgin*** paragraph 25) and the skilled reader would not think the references to the PIL in the patent were intended to alter that. Also the patent contemplates the PIL is a direction to a doctor, which it might or might not be in practice.

132. The approach of Lilly and its advisers to this issue has been casual. There was an attempt to blame the claimants for it, and for a lack of disclosure, but these problems are not the fault of the claimants at all. They arise from reading what is a copy of Lilly's own SmPC against the claims.

133. What a mess. Rather than throw up my hands, in order to try and resolve the issue of construction I will return to fundamental principles. The claim should be given a purposive construction, understanding the inventor's purpose by reading the patent as a whole. The invention presented in the patent specification is the discovery that tadalafil can be administered at low doses in a manner which is still clinically effective but also has low adverse side effects. This is said to be surprising in that the side effects were thought to be concomitant with efficacy of a PDE5 inhibitor. Doses of 2.5 and 5 mg/day are said to exhibit this property and claim 1 sets the upper limit of the daily dose at 5mg.

134. The patent specification is not suggesting that higher doses of tadalafil are not safe and effective treatments for ED. A 10mg daily dose is also fully efficacious and has minimal side effects (paragraph [0074]). The patent also teaches that doses of 25 mg and above are efficacious albeit that the adverse events must be considered (paragraph [0086]). The table in paragraph [0085] shows the skilled reader that doses of 25 mg to 100 mg give higher IIEF scores than doses below 25 mg. The table states these scores are statistically significant (presumably that is a pairwise comparison with placebo rather than a statement that the difference in score between drug treatment arms – see paragraph [0082]).

135. I will approach the matter of construction focussing on claim 7 or 10 since they include the clinical indication. For this purpose the focus is not on the part of the claim concerned with how much drug is in the tablet, it is on dosing. Subject to the word "maximum", a skilled reader would understand that what the inventor was using the words of those claims to mean is that the invention is concerned with treating sexual dysfunction by administering a dose of no more than 5mg tadalafil per day to a patient. Doing this provides the efficacy with minimal side effects provided for in the patent. Again subject to the word "maximum", the skilled reader would not think the inventors intended to exclude the idea that higher doses of tadalafil could be administered to patients if the doctor (and clinical regulators) regarded the balance of efficacy and side effects to be acceptable. Those higher doses would just not be taking advantage of the invention. So marketing authorisation documents from the regulators which approved doses of 2.5 mg per day or 5mg per day as well as 10 mg per day would not mean that a use in accordance with the invention had not been approved by the regulator. On the contrary. It would have been. Both a dose of 2.5 mg per day and a dose of 5 mg per day would take advantage of the discovery presented by the patent.

136. What then of the word "maximum"? The phrase in both claims is "administration up to a maximum total dose of 5mg *[…]* per day". The language is being used to mean that the claim does not purport to cover administration of higher daily doses. The maximum referred to is the total dose of 5 mg bearing in mind that a doctor may administer "up to" a total dose of 5mg. So if the regulators only approved 20 mg daily tadalafil then (assuming there is no off-label use) the claim would never be infringed. But if the regulator approved both 20 mg daily tadalafil and also 5 mg daily tadalafil then the latter use would infringe and the existence of the additional higher approved dose would make no difference. The claim refers to a population in that sense.

137. Having arrived at this construction of the claims, I may as well conclude the related aspect of infringement. Administration of tadalafil up to a maximum total dose of 5mg per day is one of the approved dosing regimes provided for by the regulators. It is not the only one and dosing up to higher maximum total doses which are outside the claims are also approved. However given the approval of 5mg daily dosing, I find that the use of tadalafil 2.5 mg and 5 mg tablets in accordance with the SmPC would infringe claims 7 and 10. If the relevant claimants were to launch their 2.5 mg and 5mg tadalafil tablets on the

UK market based on these marketing authorisations, the claims will be infringed.

Priority -181

138. Section 5(2) of the 1977 Act provides that an invention is entitled to priority from a priority document filed before the patent application if it is supported by matter disclosed in the priority document. The equivalent provision in the EPC is Art 87(1) which provides that the right of priority arises as long as the priority document is in respect of the "same invention". Although the language used is different, it must be taken to mean the same thing (***Unilin v Berry Floor*** [2005] FSR 6 at [39]).

139. As the Court of Appeal made clear in ***MedImmune v Novartis*** [2013] RPC 27 at paragraphs 151-154 the approach to considering whether the 'same invention' has been taught is not formulaic but is a matter of technical disclosure, explicit or implicit, and that the important thing is whether the disclosure as a whole is enabling and effectively gives the skilled person what is in the claim. The Court is not concerned with what is made obvious by the priority document - see ***HTC v Gemalto*** [2014] EWCA 1335 (Civ) at [65].

140. In ***Samsung Electronics Co Ltd v Apple Retail UK Ltd*** [2013] EWHC 467 (Pat) Floyd J (as he then was) summarised the task of the court in the following way:

> (a) to read and understand, through the eyes of the skilled person, the disclosure of the priority document as a whole;
>
> (b) to determine the subject matter of the relevant claim;
>
> (c) to decide whether, as a matter of substance not of form, the subject matter of the relevant claim can be derived directly and unambiguously from the disclosure of the priority document.

141. I agree with that summary and in particular with the emphasis on the decision being a matter of substance not form.

142. One of the priority points is concerned with ranges and sub-ranges. I will address the law on that in context.

The priority document

143. Turning to the disclosure of the priority document, the first point to note is that it is not focussed on a single compound. The very first sentence refers to phosphodiesterase inhibitors (plural) and while that might usually be a minor matter, after a passage drawing attention to the significant commercial success of sildenafil but the existence of drawbacks in terms of side effects (the PDE6 point about colour vision, flushing, and the contraindications with organic

nitrates), an important passage appears at page 3. The key thing is to use a "selective PDE5 inhibitor". It is a defined term. The priority document explains that a selective PDE5 inhibitor for oral human use has been obtained through clinical studies and the discovery that a selective PDE5 inhibitor meeting certain criteria allows for effective administration at a dose of 1-20 mg without contraindications, with a reduced tendency for flushing and with insignificant interaction with organic nitrates. The definition on page 5 corresponds to the criteria on page 3. A selective PDE5 inhibitor must have a 100 fold differential in the IC_{50} for PDE5 v PDE6, at least 1000 fold differential in IC_{50} for PDE5 v PDE1c and an IC_{50} against PDE5 of less than 10 nM. Moreover, as the claimants emphasise, the priority document states in terms that selective PDE5 inhibitors "vary significantly in chemical structure and their use in the present invention is not dependent on the chemical structure but rather on the critical parameters outlined herein." The critical parameters referred to are the three IC_{50} criteria about potency against PDE5 and selectivity as between PDE5 and PDE6/PDE1c. Consistent with this, claim 1 in the priority document claims a selective PDE5 inhibitor in a dosage form from 1-20 mg as a product and claim 9 claims the use of such a product to treat sexual dysfunction.

144. After some general discussion the priority document includes an important passage bridging pages 6 and 7 on dosage forms and dosing, as follows:

> "The package insert also provides instructions to administer one or more 1 to 20 mg dosage forms as needed up to a total dose of 20 mg per day. Preferably, the dose administered is 5 to 20 mg/day; more preferably 5 to 15 mg; and most preferably a 10 mg dose form administered once per day, as needed."

145. The priority document then refers to sexual dysfunction, including male erectile dysfunction and at page 8 (ln 25) picks up to discuss in detail the point that the invention is based on detailed experiments and clinical trials by the Applicant. At page 9 ln 16 the priority document states:

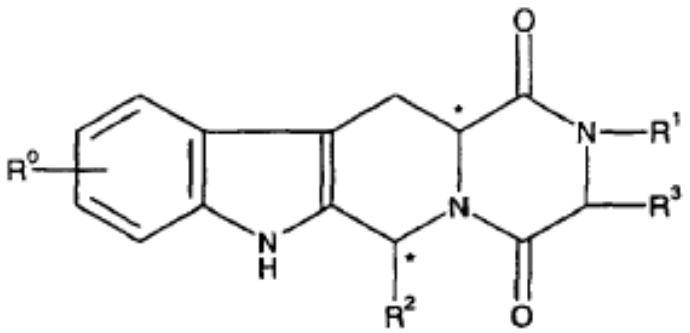
> "One such inhibitor, (6R-trans) -6- (1, 3-benzodioxol-5-yl) - 2, 3, 4, 7, 12, 12a - hexahydro-2-methyl-pyrazino [1',2':1,6]-pyrido [3,4-b] indole-1,4-dione, was demonstrated in human clinical studies to have minimal impact on systolic blood pressure when administered in conjunction with nitrates. By contrast sildenafil demonstrates a 4 fold greater decrease in systolic blood pressure over placebo, which leads to the contraindications and warnings in certain patients."

146. The first issue with that chemical name is that it contains an error. The numeral 4 in the run of numbers referring to the six hydrogens (hexahydro) should be a 6 so that the chemical name should read: (6R-trans) -6- (1, 3-benzodioxol-5-yl) - 2, 3, 6, 7, 12, 12a - hexahydro-2-methyl-pyrazino [1',2':1,6]-pyrido [3,4-b] indole-1,4-dione. It was common ground that this

error has no consequences. It would not cause the skilled reader to misunderstand the name. They would correct it.

147. The second issue about the chemical name is a major dispute between the parties. Lilly, supported by Prof Donohoe, contends the chemical compound named there is the compound now called tadalafil. The claimants, supported by Dr Gibson, submit the name refers to a different compound which is not tadalafil. The argument is about what "(6R-trans)" means in this context. The two rival compounds are stereoisomers. Only one is tadalafil. The term "Named Compound" was used at trial to refer to whatever is named by that chemical name. Putting the debate to one side at this stage, what the priority document has taught here is that the Named Compound has been tested and has an advantage over sildenafil relating to blood pressure and nitrates. The Named Compound is also "one such inhibitor" which means it is a selective PDE5 inhibitor, i.e. it meets the three IC_{50} criteria. So the tests on the Named Compound support the hypothesis on which the general teaching of the priority document is based.

148. From here the priority document repeats the point that selective PDE5 inhibitors vary significantly in chemical structure and that the invention is not dependent on the chemical structure but on the critical parameters. Then the document moves into discussing preferred compounds by reference to earlier disclosures including US patent 5,859,006 and others. Generalised structures of preferred compounds from the 006 patent are mentioned based on what the priority document identifies as Formula (I):



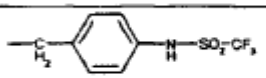
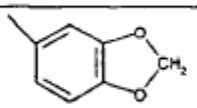
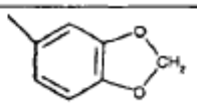
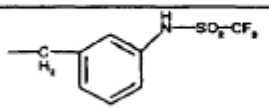
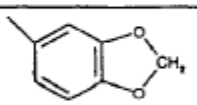
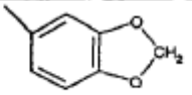
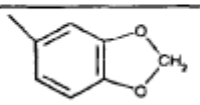
(I)

149. Details of possible substituents are given and then the priority document sets out a table of potency values and ratios for five compounds which are said to be within the disclosure of the 006 patent and are representative selective PDE5 inhibitors. The table is:

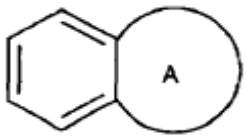
Table 1			
Compound	PDE5 IC_{50} (nM)	PDE6 IC_{50} (nM)	PDE6/PDE5
1	5	663	133
2	2	937	469
3	2	420	210
4	5	729	146
5	2.5	3400	1360

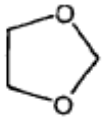
150. After the table the priority document states that "Compound 5 additionally demonstrates an IC_{50} against PDE1c of 10,000 and a ratio of PDE1c/PDE5 of 4000".

151. The document then explains that the structures of Compounds 1 to 5 in Table 1 are given in another table, which is not numbered but which I will call Table 2. It is:

Compound	R^0	R^1	R^2	R^3
1	H			H
2	H	CH_3		CH_3
3	H			H
4	H	CH_3		H
5	H	H		CH_3

152. After this table the priority document states:

> The data in Table 1 indicate that a compound of Formula (I), wherein R^1 is hydrogen or C_{1-6} alkyl, R^2 is
>
> 
>
>
> and R^3 is hydrogen; is especially preferred. Preferably A is



153. As Table 2 is written, the Named Compound would be Compound 4 or to be precise it would be an individual stereoisomer within the formula given for Compound 4. Table 2 does not distinguish between stereoisomers although the skilled reader would assume that the compounds tested were in all probability single stereoisomers rather than racemates.

154. The third issue and another major area of dispute is about what the skilled reader would make of Table 2 and the text around it. Lilly, supported by Prof Donohoe, contends that the reader would appreciate an error must have been made and also perceive what should be done to correct it, which is that the substituents in the table for compounds 4 and 5 had been swapped. When the error is corrected the result is that Compound 5 is equated with the Named Compound. The claimants, supported by Dr Gibson, deny the skilled reader would think there was an error and deny that even if they did, the correction is the one proposed by Lilly either at all or sufficiently clearly to be relevant.

155. After this from p12-13 the priority document sets out a list of five preferred compounds. Whatever else they are, they all include a benzofuranyl group as the group defined as A above which means that none of them can be any of compounds 1-5 nor can they be the Named Compound. The stereochemistry of these compounds is defined. No experimental data for these benzofuranyl compounds is given either there or elsewhere in the priority document.

156. Next, from p13 to p20 further additional exemplary and preferred compounds are described by reference to other published patent applications. After that is a section describing preparations of PDE enzymes and how to conduct IC_{50} measurements. Then at p28 the examples start. Example 1 is a formulation example said to be of a compound within the 006 patent which is a selective PDE5 inhibitor but not otherwise identified. Examples 3 and 4 are formulations of an unspecified selective PDE5 inhibitor. Example 4 describes a clinical study in healthy male volunteers of concomitant administration a drug described as "Study drug" which is a selective PDE5 inhibitor together with short-acting nitrates and measurement of blood pressure. The Study drug is given at a daily dose of 10mg. The example reports that the Study drug was well tolerated with no adverse events. The skilled reader would clearly associate this with the statement on page 9 that the Named Compound had been tested and shown an advantage over sildenafil relating to blood pressure and nitrates. It was common ground that the reader would assume the Study drug was the Named Compound. This example is in effect part of a Phase I study of the Named Compound. It is not and does not purport to be a study of efficacy.

157. Finally the priority document sets out Example 5. This example describes two clinical studies of erectile function in patients. Both on demand and daily dosing are studied. The example reports that the drug is efficacious with

minimal side effects (<1% flushing and no reports of vison abnormalities). The compound used in the example is identified as Compound 5.

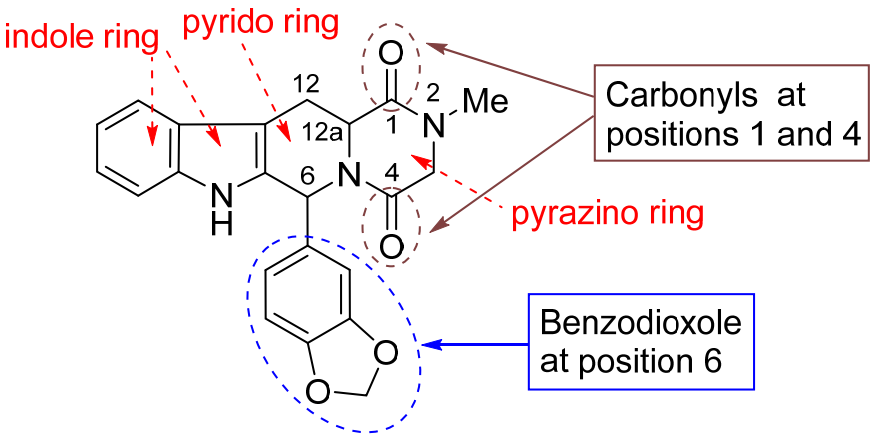
158. Then there are the claims which refer to a selective PDE5 inhibitor and in which the only compounds specifically named are the benzofuranyl compounds.

159. Overall Lilly's case is that the Named Compound would be understood to be Compound 5 and so both Examples 4 and 5 would be understood to relate to the same compound, which is the one now called tadalafil. Lilly contend this conclusion is one which would make sense to the skilled reader taking the document as a whole. The claimants disagree as I have explained. They contend that the reader would not be surprised to find results from trials of two different compounds being described. One is the Named Compound, aka Compound 4, and has been tested in Example 4. It is not tadalafil but a different stereoisomer of the same basic structure. The other is Compound 5, which is a different compound from tadalafil altogether. The stereochemistry of Compound 5 is not defined.

Is the Named Compound tadalafil?

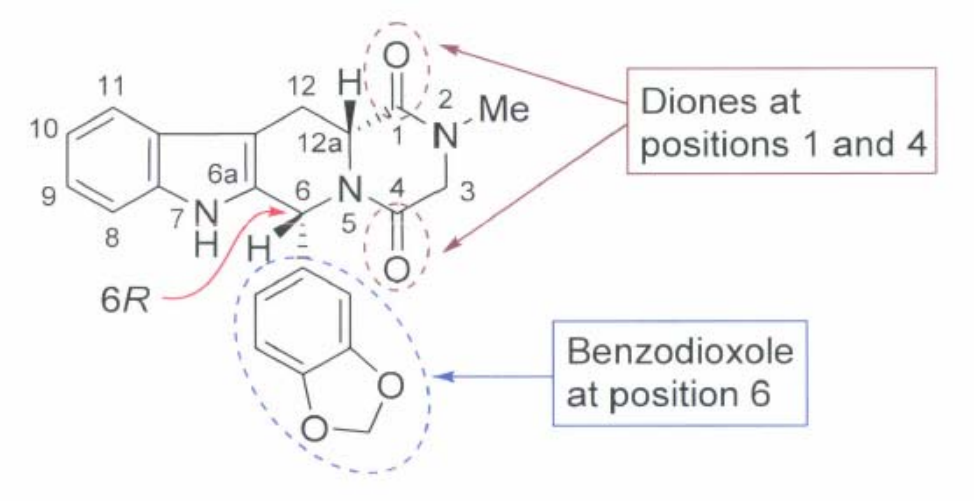
160. In order to identify the Named Compound, one needs to decode the chemical name on page 9. Chemical names are constructed according to internationally agreed rules which chemists know. Whether chemists who make a special study of the nomenclature know all the rules is not relevant. The relevant person is the medicinal chemist member of the skilled team. Those people do not know all the rules or anything like it. An important point in my judgment, having listened to the evidence of Prof Donohoe and Dr Gibson, is that the proper application of the nomenclature rules to a given case involves a matter of chemical judgment. I will return to that below.

161. It is common ground that decoding the chemical name on page 9 apart from the term "(6R-trans)" produces the following chemical structure:



162. This diagram is taken from Lilly's skeleton argument. The key thing is that this is a structure shown without stereochemistry. I will call it the general structure. The medicinal chemist would have no difficulty getting this far and would perceive that this molecule has two chiral centres. One is the carbon at

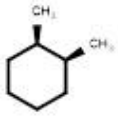
the 6 position and the other is the carbon at position 12a. There are hydrogens at positions 6 and 12a (and elsewhere) but by convention they are not drawn. The medicinal chemist would also know that "(6R-trans)" is the term in the name which is intended to define the stereochemistry of the molecule within the general structure which is being referred to. There are two options, as the medicinal chemist would understand. One possible stereoisomer is the following:



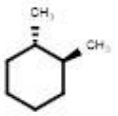
(the labelling in the boxes can be ignored)

163. The key thing is that in this diagram the benzodioxole group attached to position 6 is shown as oriented downwards by the dashes while the hydrogen at position 12a is shown as upwards by the heavy wedge. This stereoisomer is tadalafil. The other possible stereoisomer would have the orientation at 12a swapped over so that the hydrogen there is oriented downwards, in the same orientation as the benzodioxole group. Drawn as above there would be dashes connecting the hydrogen to position 12a and a heavy wedge connecting 12a to the carbonyl carbon at position 1. There are in fact two other stereoisomers which would be within the general structure, both of them having the benzodioxole group oriented upwards. However they are excluded by the term "6R" which, by applying the chemical naming rules, unambiguously identifies the molecule as one with the benzodioxole group pointing downwards and the hydrogen upwards at position 6, as shown. Those other two stereoisomers would be "6S" rather than "6R".

164. The question is about the word "trans". The terms "cis" and "trans" are familiar aspects of chemical nomenclature. "Cis" means the same side and "trans" means across or on the opposite side. Dr Gibson gave an example for monocycles in his first report:



cis-1,2-dimethylcyclohexane



trans-1,2-dimethylcyclohexane

165. It is common ground that the usage "(6R-trans)" (or "(6R-trans)-6-") would be seen as unusual by the medicinal chemist but they would nevertheless understand that "trans" in the term must refer to the stereo-chemical relationship between the benzodioxole group at position 6 in the 6R case with an atom bonded to the carbon at the other chiral centre, i.e. at 12a. The question is which atom bonded to 12a does the term "trans" refer to? There are two and only two possibilities but they produce opposite results. The Named Compound is the one in which the correct atom bonded to 12a is trans with respect to the benzodioxole group at position 6 in the 6R. If the correct atom is the hydrogen then the compound is tadalafil. If the correct atom is the carbonyl carbon at position 1 then the Named Compound is not tadalafil but something else. Named in an alternative naming convention, Lilly contends the Named Compound is (6R, 12aR) whereas the claimants contend the Named Compound is (6R, 12aS).

166. The general rules of chemical naming are the IUPAC Blue Book rules. There is no dispute that none of those rules expressly address the particular situation which would arise. That is important but it cannot be taken too far. The medicinal chemist knows that the rules cannot cater expressly for every conceivable possibility.

167. The two experts' opinions about what conclusion the medicinal chemist would reach were in conflict.

168. Dr Gibsons' opinion was that the correct atom was the carbonyl carbon. The key to his reasoning is that to work out which substituent at a chiral centre is the one referred to, one applies the Cahn Ingold rules of priority based on atomic number. Carbon has a higher atomic number and therefore higher priority than hydrogen and so the carbon is the one. It is the carbonyl carbon at position 1 because what the medicinal chemist would do is apply the cis and trans names as they are applied to monocycles as shown above. The relevant ring is the pyrido ring which contains both chiral centres. Applying the rules this way the medicinal chemist would identify the carbonyl carbon at 1 to be trans with respect to the benzodioxole group. Dr Gibson supported this by reference to the preamble to IUPAC rule E3 which is as follows:

> "**Fused rings**. In simple cases the relative stereochemistry of substituted fused-ring systems can be designated by the methods used for monocycles. For the absolute stereochemistry of optically active and racemic compounds the sequence-rule procedure can be used in all cases (see Rule E-4.9 and Appendix 2); for relative configurations."

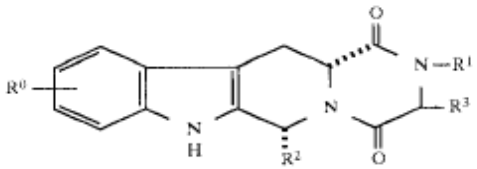
169. The significance of this is that the general structure of the Named Compound is undoubtedly a fused ring. Dr Gibson's point is that the first sentence here refers back to the methods used with monocycles. The detailed parts of rule E3 do not apply to the Named Compound. Lilly referred to sub-rule E3.1 which is as follows:

> "E-3.1. Steric relations at saturated bridgeheads common to two rings are denoted by cis or trans. followed by a hyphen and placed before the name of the ring system, according to the relative positions of the exocyclic atoms or groups attached to the bridgeheads. Such rings are said to be cis-fused or trans-fused."

170. Lilly's point is that this indicates that what is to be cis or trans with respect to one another are the exocyclic atoms or groups. At position 6 the correct exocyclic group is clearly the benzodioxole group but at position 12a the carbonyl carbon is not an exocyclic atom. It is within the fused ring structure. The only exocyclic atom at 12a is the hydrogen. So trans refers to that and hence the compound is tadalafil.

171. Dr Gibson did not agree that rule E3.1 applied since it expressly refers to steric relations at saturated bridgeheads common to two rings. I accept Dr Gibson's evidence that the two chiral centres in the Named Compound are not at a saturated bridgehead. The Named Compound is not one where the two chiral centres are two bridgehead atoms.

172. Before turning to Prof Donohoe's opinion it is convenient at this stage to refer to the 006 patent. Dr Gibson supported his opinion by reference to that patent, which the priority document expressly refers to, purports to incorporate by reference and explains that the Named Compound is within. The 006 patent states (col 4) that a preferred (in 006) group of compounds are the "cis isomers" of the following formula:



173. One of them is named as (6R,12aR) - 2, 3, 6, 7, 12, 12a - hexahydro -2-methyl -6- (3, 4-methylene dioxyphenyl) pyrazino [2', 1' : 6, 1] pyrido [3, 4-b] indole -1,4- dione. That is tadalafil. Instead of the usage "(6R-trans)" this name uses the term "(6R, 12aR)" which unambiguously makes it the stereoisomer which is tadalafil. Dr Gibson's point is that since the (6R, 12aR) compound is called the cis isomer in the source document which the priority document expressly refers to, that would support the medicinal chemist's conclusion that the Named Compound with the designation (6R-trans) must be the other isomer i.e. (6R, 12aS).

174. Lilly's case, supported by Prof Donohoe, was that the 006 patent would be understood in a different way. The 006 patent describes the synthesis of

various compounds including the (6R, 12aR) compound (i.e. tadalafil). A key synthetic step is to start with an intermediate compound in which what becomes the pyrazino ring is open and has to be closed. The expression cis is derived from the fact that in the ring open configuration the intermediate is indeed a cis isomer (col 16 ln50). Prof Donohoe gave this example of one of the intermediates:

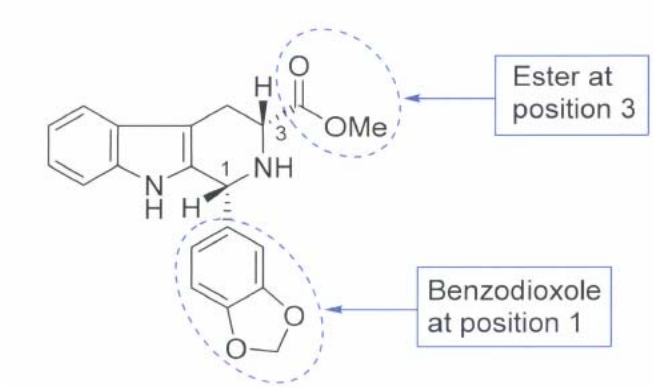


Figure 3: Intermediate 54

175. When the pyrazino ring is closed (assuming the correct closure and preserving the stereochemistry) the result is the (6R, 12aR) compound (i.e. tadalafil). Prof Donohoe's opinion was that the correct application of the IUPAC rules calls the intermediate "cis" but would call the final compound with the same stereochemistry "trans" and the reader would conclude that the authors of 006 had adopted a local rule for internal consistency, which he said was commonly done in chemistry. He was cross-examined on the basis that the examples of the adoption of local rules he relied on were clear whereas the 006 patent says nothing express about a local rule. While that reduces the force of Prof Donohoe's point, in my judgment it does not extinguish it. A medicinal chemist who considered the 006 patent would see that the origin of the reference to cis was in the intermediates. If they noticed the reference to cis in 006 at all, they might well conclude the usage in the 006 patent was adopted for internal consistency

176. In my judgment the 006 patent does not materially assist the claimants' argument. The 006 patent does not use the same chemical naming convention as the priority document. The term "(6R-trans)" is not used. I doubt a medicinal chemist who had identified which stereoisomer the Named Compound was would think to scrutinise the 006 patent to see if they had the reached the right result. If they did take that step they would see two things. First they would see that the (6R, 12aS) version of the general structure of the Named Compound is not expressly referred to at all. The isomer identified in 006 is (6R, 12aR). Second they would see the reference to cis isomers. A skilled person who was in doubt about the Named Compound would still be in doubt. The first point favours Lilly but not strongly because both isomers are within the generality of 006 and the second point favours the claimants but not strongly because it could well be terminology adopted for consistency. On the

other hand a skilled person who had reached a conclusion reading the priority document would not be caused to change that conclusion reading 006.

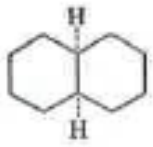
177. Coming back to the priority document itself, Prof Donohoe's reason for disagreeing with Dr Gibson was that the medicinal chemist would first identify the exocyclic substituent(s) at position 12a as the substituents to which the designation trans applied. If there were two the atomic number priority would apply but the only exocyclic substituent at 12a is the hydrogen. Therefore that is the atom which must be trans with respect to the benzodioxole group at position 6. The carbonyl carbon at position 1 is not relevant because is forms part of the fused ring structure. It is not exocyclic. His opinion was that rule E3.1, although as written is only applicable to saturated bridgehead atoms, was an example of this wider principle that exocyclic substituents in fused rings were the ones to be considered.

178. The Professor's opinion was that the medicinal chemist would always treat the fused ring structure as a whole as planar and would consider the cis and trans designations as referring to the orientation of exocyclic substituents above or below the notional plane of the fused ring system. It was put to him that in a drawing of the structure in his report the Professor had included a dashed line internally within the fused ring and that showed he did not regard the fused ring as planar. In my judgment there was a minor inconsistency here but it does not significantly undermine the Professor's evidence. His point was not that the chemist would think or assume the ring actually was planar. His point was that the chemist would know it was not planar but nevertheless treat it as such for the purposes of assigning cis and trans orientations to exocyclic substituents.

179. Prof Donohoe accepted that the rules did not expressly contain a provision written in the same level of generality as he expressed himself but maintained that that was how a medicinal chemist would apply their understanding of the naming rules. His opinion was that Dr Gibson's approach was incorrect and unreasonable.

180. In chief the Professor explained by reference to structures drawn out on a sheet X2 that if the rule was applied to include endocyclic substituents as Dr Gibson contended the naming risked being ambiguous. If endocyclic substituents were taken into account the same compound could be cis and trans depending on which of the two rings of the fused ring structure one started with, whereas the problem does not arise if only exocyclic substituents are considered. I accept that evidence at least as it applies to two chiral centres at bridgeheads but I note that the Named Compound is not one of those.

181. Prof Donohoe referred to the naming of the compound cis-Decalin in rule E3.1, which is:



cis-Decalin

182. When challenged he maintained that an ordinary chemist faced with the Named Compound would have to think about it but would draw an analogy with the saturated bridgehead referred to in rule E3.1 and the naming of cis-decalin.

183. The claimants relied on the fact that in cross-examination Prof Donohoe accepted that his application of the rules to the Named Compound was an extension of rules E3.1 and was not common general knowledge. The claimants placed emphasis on this evidence but it does not support their case in the way they contend. The Professor's opinion was clear in that he regarded his approach as a very simple and logical extension of the express rules and one which the skilled person would adopt. His answer about common general knowledge was that the extension would not be within the common general knowledge of a chemist. In saying this the Professor did not mean to qualify his opinion that a skilled chemist would apply his chemical judgment when faced with the Named Compound in the manner he contended for, it was a reflection of the fact that the rules cannot cover every possible eventuality because there are so many different combinations in chemistry.

184. Prof Donohoe also supported his view with other examples. Certain cephalosporin antibiotics are named using the expression (6R-trans) in the context of a fused ring structure in the same way as Prof Donohoe contends would be done and notwithstanding that the (6R-trans) designation refers to one substituent which is not a saturated bridgehead common to two rings. The point is not that the naming of these cephalosporins would be part of the common general knowledge. The point is that chemists have exercised their chemical judgment in an analogous situation and applied the naming rules in the manner contended for by Prof Donohoe.

185. By contrast no examples were produced in evidence by the claimants in which "(6R-trans)" or something equivalent to it had been interpreted in the manner they contended for. The closest is the reference to cis isomers in the 006 patent but that is not the same usage as in the priority document. Another reference, omitted from the draft judgment, is in US 6,890,933 (see pages 17 and 20 and see T2/p26$1_{14}$-26$3_{5}$) but that too is like the usage in the 006 patent and is not the same usage as in the priority document.

186. It was suggested that Prof Donohoe's view was tainted with hindsight because he had known before he read the priority document that the target was tadalafil. I have taken that into account but in the end what matters are the reasons an expert gives for their opinion rather than the fact they hold it. The cephalosporin example involves no hindsight.

187. Lilly sought to rely on hearsay evidence concerning the use of the (6R-trans) name for tadalafil in Chemical Abstracts. The inference they invited the court to draw was that it was the expert staff at Chemical Abstracts who had coined the (6R-trans) name for the compound after it was published in the Daugan prior art. The materials relied on do not support that inference. The one inference which I can draw from those materials and the other materials in this case is that the (6R-trans) name was coined by someone to refer to the compound now called tadalafil, i.e. the (6R-12aR) compound. I am quite sure it was never intended to refer to the (6R-12aS) isomer. However that is not a piece of information which would be available to the skilled reader of the priority document.

188. Some further support for Prof Donohoe's approach comes from the behaviour of the Chemdraw software package. In his first report Prof Donohoe explained he had entered the name into Chemdraw and the software had produced the compound which is tadalafil. In reply Dr Gibson challenged the ability of the form of Chemdraw software available at the priority date to undertake this task. Following this no case was advanced by Lilly that the skilled team would use Chemdraw at the priority date. However the fact remains that the Chemdraw software does produce the tadalafil structure when presented with the (6R-trans) name. Lilly's counsel put this to Dr Gibson in cross-examination on the basis that Chemdraw works by applying the chemical nomenclature rules and so this supported Lilly's case. Dr Gibson suggested that perhaps Chemdraw used a look-up table for pre-existing names. Since today the (6R-trans) name is associated with tadalafil, that could explain the behaviour of Chemdraw. However I find that Chemdraw is not using a look up table but rather has derived the tadalafil structure by applying the chemical nomenclature rules. That is for two reasons. First it is consistent with the way Chemdraw is described in its own literature. Second, as Prof Donohoe showed in his evidence, if the same name is used but with the designation (6R-cis) instead of (6R-trans) Chemdraw produces the (6R-12aS) stereoisomer. The (6R-cis) name has not been used before and so that cannot be the result of a look up table in Chemdraw. So Chemdraw's application of the naming rules is consistent with Prof Donohoe's opinion and inconsistent with Dr Gibson's.

189. Standing back, the question I need to ask is what would the medicinal chemist member of the skilled team make of the name of the Named Compound? If they would interpret it as Dr Gibson did or if they are left with any material doubt about how to interpret it, then there is no clear and unambiguous disclosure of tadalafil. If they would interpret it as proposed by Prof Donohoe then tadalafil is disclosed.

190. I prefer the reasons given by Prof Donohoe to those of Dr Gibson. The cephalosporin examples support the Professor and so does Chemdraw. As I have already said, the 006 patent does not assist the claimants' argument. I find that the medicinal chemist would apply the trans designation in (6R-trans) to the hydrogen at the 12a position because it is the exocyclic substituent in a fused ring system. They would know the rules did not expressly provide for the situation they were faced with but they would have no real difficulty

dealing with the formula. They would not think it was sensible to apply that designation to the endocyclic carbonyl atom at position 1. It would not be reasonable to apply that sort of stereochemical descriptor to atoms inside a fused ring structure when the possibility of applying it to an exocyclic atom existed. I find that the Named Compound would be identified as the stereoisomer which is tadalafil.

191. I should make clear that the complex reasoning and consideration of the evidence above which I have gone through in order to decide how the skilled person would think is different from the thought process of the skilled person themselves. Based on all that evidence, I have concluded that they would apply the trans designation to the hydrogen at 12a without major difficulty.

What are Compounds 1 to 5?

192. The next problem is what to do about Table 2. The first issue is whether the skilled reader would notice anything amiss at all. In my judgment they would, for the following reasons.

193. Although all five of Compounds 1 to 5 are within the class "selective PDE5 inhibitors" it is striking that Compound 5 is the only one for which actual experimentally derived data is given for all three criteria which the document explains are important. Data for two criteria are reported in Table 1: the IC_{50} for PDE5 and the ratio PED6/PDE5, but the third criterion is the ratio for PDE5 vs PDE1c. It is common ground that based on Table 1, Compound 5 would be of particular interest. Compound 5 is reported to have a ratio of 4000 in the text after Table 1 but no other statement is made for Compounds 1 to 4. The reader would infer there must be at least a 1000 fold differential for each otherwise they would not be "selective PDE5 inhibitors" but that is all. The fact that Compound 5 is tested in Example 5 also adds to the emphasis placed on it.

194. Prof Donohoe said that Compound 5 is the only compound in Table 1 said to satisfy all three criteria but, as the previous paragraph explains, that is an overstatement. All five compounds in the table are said by the document to satisfy all three criteria but only Compound 5 has a reported value (or "hard data") relevant to the third criterion.

195. Immediately after Table 2 the document refers to an "especially preferred" compound and states in terms that it is the data in Table 1 which indicate the compound is especially preferred. The sentence appears to refer to a single compound but the definition is actually a class. In any event the only compound in the class as written which is in Table 1 is Compound 4. That is due to the defined substituents R^1 and R^3. However, the data in that table do not indicate that Compound 4 is especially preferred. On the contrary. Compound 4 is one of the two least potent inhibitors of PDE5 in the table and one of the two least selective inhibitors for PDE6 with a PDE6/PDE5 ratio of 146. So by the criteria which characterise a selective PDE5 inhibitor in Table 1, singling out Compound 4 is very odd. In the abstract the idea that Compound 4 might be a compound which the inventors especially preferred for some other reason would not be odd at all. What is peculiar is the

statement that it is the data in Table 1 which indicate that such a compound is especially preferred. So the skilled reader will see that there is something wrong somewhere.

196. However just spotting there is a problem does not mean the skilled reader necessarily would embark on trying to fix it nor does it mean that any particular fix is so clear as to be relevant to the legal questions I have to decide.

197. Pausing at this stage in the reasoning, and looking at the document as a whole, on the face of it the skilled reader sees the following. Although other compounds and classes of compounds are discussed, emphasis seems to be placed on two particular compounds. One is Compound 5. This is the only one for which experimentally derived results for all three criteria are reported. Compound 5 has been tested in patients (Example 5) and found to be fully efficacious with minimal side effects in doses from 5 to 20 mg. But no stereochemistry is defined for Compound 5 even though the skilled reader would assume that a particular stereoisomer was being discussed. Based on Table 1, Compound 5 has the highest PDE6/PDE5 selectivity ratio (Table 1) and high potency against PDE5 (2.5nM). The other is the Named Compound/Compound 4. This is a "selective PDE5 inhibitor" as defined. It has a higher PDE6/PDE5 selectivity ratio than sildenafil (compare priority document p2 ln15). It has been tested in Example 4 in healthy volunteers and found to have minimal effect on blood pressure in conjunction with nitrates. Its stereochemistry is defined.

198. Lilly's case, supported by Prof Donohoe is that the skilled person would realise that a clerical slip had been made in drafting Table 2 and that the substituents in the two rows of the table for compounds 4 and 5 had been swapped. Swapping them back again allows the sentence after Table 2 to make sense because the compound in Table 2 which the sentence referred to would now be Compound 5 and the data in Table 1 does indeed indicate that Compound 5 is especially preferred. As a consequence the compound called Compound 5 would also be the Named Compound (i.e. tadalafil). And so Example 5 would also be a test of tadalafil as well as Example 4.

199. It was common ground between Prof Donohoe and Dr Gibson that three different options could be identified which were possible ways of dealing with the perceived inconsistency between the text after the tables and the data in the tables. The options are (i) to swap the rows in Table 2 for Compounds 4 and 5, (ii) to swap the values in Table 1 for Compounds 4 and 5, or (iii) to add the words "C1-6 alkyl" after "R3 is hydrogen" in the sentence after Table 2. There is no doubt that all three remove the inconsistency.

200. Option (i) is Lilly's case. Options (ii) and (iii) make the text consistent but leave Compounds 4 and 5 as different chemical entities. Taking either option (ii) or (iii) leaves the Named Compound/tadalafil as Compound 4.

201. Prof Donohoe's view in his report was that option (i) would be chosen however there are aspects of Prof Donohoe's reasoning which do not bear the weight placed on them by Lilly. One was his view that Compound 5 is the

only compound in Table 1 said to satisfy all three criteria. I have addressed that already.

202. A second aspect was his view about the relevance of the link between the 006 patent and the priority document to this aspect of the matter. This has two elements. The first element was the fact that a compound I will call "Compound 5 (R^3=methyl)", in other words the compound which Table 2 as drawn identifies as Compound 5, is not specifically identified in the 006 patent. That is true but not very significant. All the compounds 1 to 5 are within what is disclosed in the 006 patent. The skilled reader reading the priority document would assume all five compounds had been made since IC_{50} vales for each are reported. If the Compound 5 (R^3=methyl) compound really should be called Compound 4, which is Lilly's case, it is still a compound within the 006 patent which the priority document teaches has been made and tested albeit the 006 patent does not specifically identify it. The reference on p9 ln30 to compounds being "readily identified" from the 006 patent does not help nor does the fact that tadalafil is a specific compound described in the 006 patent and on which emphasis is placed there.

203. The second element in the argument about 006 is that Example 1 of the priority document states (p28 ln18-19) that "compound" (unnamed) was prepared as described in the 006 patent. However the priority document is unspecific. The 006 patent describes general synthetic approaches for the class of compounds described and sets out a specific synthetic scheme for the compound now known as tadalafil. In my judgment this has no significant bearing on the question of whether a skilled reader who had realised there was something wrong somewhere in the priority document would decide that two rows on Table 2 had been swapped. If the Named Compound (tadalafil) is Compound 4 so that the Compound 5(R^3=methyl) compound is a different chemical entity then the 006 patent provides a worked example of how to make Compound 4 and a general teaching which includes Compound 5. That is not inconsistent with what is stated in the priority document. Dr Gibson did not think it was surprising that a compound which looked promising in the priority document was not specifically identified in the earlier 006 patent. I accept Dr Gibson's view on that.

204. A third aspect of Prof Donohoe's reasoning is that no stereochemistry is given for Compound 5(R^3=methyl) even though it has been tested in Example 5. I agree that the skilled reader would be conscious of this. They would wish to have been told what it was. But this cannot be taken too far. It would not be the only way in which the priority document is unforthcoming in its disclosure. The first three examples are entirely unspecific. Nevertheless it is true that of the three options, only option (i) has the result that the skilled reader would know the stereochemistry of Compound 5.

205. A further matter was a point Prof Donohoe confirmed he was not making. The claimants thought the professor was suggesting that the skilled reader would expect only one compound to have been tested in clinical studies. If such an expectation existed then it would support Lilly's case. However Prof Donohoe explained he did not make that assumption. He did not have enough experience of that kind of issue. In my judgment, particularly given the

general teaching of the priority document about selective PDE5 inhibitors regardless of structure and its emphasis on the three criteria, the skilled reader would not think it odd to see two different compounds tested in clinical studies here.

206. Lilly also submitted that the fact that tadalafil was clearly emphasised in another document referred to in the priority document is important. Lilly is right that WO 95/19978 (Daugan) and WO 96/38131 (Butler) do identify tadalafil and are referred to in the priority document at p9 ln30 and p8 ln6. However that is as far as this point goes since the Named Compound is tadalafil. It does not help decide if Compound 5 should also be tadalafil.

207. In cross-examination Prof Donohoe accepted that option (ii) (swapping values in Table 1) was a "realistic candidate". Counsel suggested in closing that this evidence went no further than the Professor's report in which he identified option (ii) as a candidate but gave reasons why the skilled reader would not adopt that option. I do not agree. One of the reasons the Professor gave for this in his report (paragraph 6.26) was that the priority document only gives PDE1c data for Compound 5. But he accepted that all five compounds meet all three criteria including the PDE1c criterion. The cross-examination sought to undermine the weight to be given to that reason and in my judgment Prof Donohoe's answer accepted that it did.

208. Prof Donohoe's reason for rejecting option (iii) was that it would make Compound 5 have the especially preferred structure but it would not make Compound 5 the compound singled out on page 9 (i.e. the Named Compound, tadalafil) which is a key compound and is specifically referred to in the cross-referenced documents. For the reasons I have already addressed, these points do not bear the weight placed on them by the Professor.

209. Dr Gibson's view was that option (iii) would make the fewest changes and might be deemed most likely by the medicinal chemist. The challenges in cross-examination to Dr Gibson were not focussed on this issue but rather were aimed at challenging his view that no inconsistency would be spotted at all and other matters.

210. Reviewing these arguments and looking at the matter as a whole, I think a skilled reader would rank option (i) before options (ii) or (iii) because it has the virtue of explaining why no stereochemistry is given for Compound 5 as written, but they would not reject the other two possibilities. A small but not trivial point is that in the clinical studies each example uses a different name for the drug being tested. Example 4 tests "Study drug" while Example 5 tests "Compound 5". If they were the same drug, one might have expected them to be given the same name. In the end the skilled reader would be left in real doubt as to what the correction was. They are all realistic and the advantage of option (i) is not strong enough to rule out the others. Accordingly, I find that the priority document does not disclose that Compound 5 is tadalafil. The reader would understand that it might be but would be left in real doubt.

Ranges

211. Claim 1 relates to a dosage form (e.g. a tablet) comprising 1 to 5 mg of tadalafil which is suitable for oral administration up to a maximum total dosage of 5 mg per day. The key disclosures in the priority document are:

i) Page 3 ln 6-7 which mentions dosage forms at dosages between 1 and 20 mg/dosage form;

ii) The passage bridging pages 6 and 7 which I have quoted already but will repeat:

> "The package insert also provides instructions to administer one or more 1 to 20 mg dosage forms as needed up to a total dose of 20 mg per day. Preferably, the dose administered is 5 to 20 mg/day; more preferably 5 to 15 mg; and most preferably a 10 mg dose form administered once per day, as needed."

iii) Example 4 in which the Study drug (tadalafil) was given to healthy volunteers at 10mg per day;and

iv) Example 5 which describes Compound 5 (which might or might not be tadalafil) with 5 to 20 mg doses and 10 to 100 mg doses in which 10 mg being preferred.

212. There are two issues: first whether a range of 1-5mg for the dose of an individual dosage form is supported and second whether a maximum total dose of 5mg per day is supported.

213. Lilly submitted that 1-5 mg was a sub-range of the range 1-20 mg and submitted as a matter of law that:

> "123. Where a priority document discloses a numerical range from which the patent claims a sub-range, the appropriate forensic question is whether the sub-range is a novel one. If it is not, then it merely forms part of the disclosure of the priority document, and the claim to the sub-range is entitled to priority."

214. In my judgment there is not a special law for priority concerning sub-ranges. As ***MedImmune*** explains the correct approach to priority in general is not formulaic but is a matter of technical disclosure reading the priority document as a whole, in the light of the common general knowledge. There is no reason to apply different tests to different kinds of disclosure. Apart from anything else while some ranges and sub-ranges are easy to identify, others are not. That would be a real problem if there was a special law for sub-ranges.

215. Lilly sought to rely on EPO cases on the novelty of sub-ranges (***T198/84***, ***T279/89*** and ***T247/91***) and justified its overall submission by reference to the Enlarged Board in ***G2/98***:

> "8.4 If the invention claimed in a later European patent application constitutes a so-called selection invention– i.e. typically, the choice of individual entities from larger groups or of sub-ranges from broader ranges of the numerical values - in respect of the subject matter disclosed in the first application this priority is claimed, the criteria applied by the EPO with a view to assessing novelty of selection inventions over the prior art must also be considered carefully when assessing whether the claim in the European patent application is in respect of the same invention as the priority application within the meaning of Article 87(1) EPC. Otherwise, patent protection for selection inventions, in particular in the field of chemistry, could be seriously prejudiced if these criteria were not thoroughly complied with when assessing priority claims in respect of selection inventions. Hence, such priority claims should not be acknowledged if the selection inventions in question are considered "novel" according to these criteria."
>
> (Lilly's emphasis)

216. I would be surprised if the Enlarged Board meant to say anything to contradict its general approach that the invention must be clearly and unambiguously derivable from the priority document and I do not believe anything in that passage does this. If a claim represents a selection invention over the disclosure of the priority document then it must be a different invention and one can see that if those were the facts, the claim ought not to have priority. But this does not mean that the converse is true. It does not mean any selection of a sub-range is necessarily entitled to priority *unless* it is a selection invention over the disclosure of the priority document. I reject that submission and, as the claimants point out, it was also rejected by Henry Carr J in ***Hospira v Cubist*** [2016] EWHC 1285 at paragraphs 114-123.

217. Nevertheless decisions on the novelty of sub-ranges will inevitably involve addressing the question of whether a sub-range is or is not disclosed in certain circumstances. That is relevant to the enquiry into priority but it does not mean priority is a novelty test.

218. Turning to the facts, the key passage is the one at p6-7. It refers to a selective PDE5 inhibitor in general. The reader would understand it to relate to the Named Compound (tadalafil) as much as to any other.

219. The parties' arguments involved some elaborate verbal analysis and so this part of the judgment necessarily has to do so too in order to explain my conclusions. The first issue is the maximum total dose of 5mg per day referred to in claim 1.

220. I think the claimants at times suggested that the lower doses in the second sentence in the quoted passage (above) were still governed by a maximum of 20 mg in the first sentence but I do not agree that that is the correct way to read the document. The second sentence would be understood to contain narrower alternatives to the upper limit of the total dose to be administered which is disclosed in the first sentence.

221. The claimants also suggested that in effect what was ruled out by the first two clauses in the second sentence was total doses below 5 mg per day. Or arguing in a different way, the first sentence only referred to a total dose of 20 mg as a maximum across a population (returning to the issue of construction). So if a doctor gave one patient (say) 3 mg per day, another 15 mg per day and a third 20 mg per day the doctor would still be working within the first sentence because the global maximum there was still 20 mg per day. Whereas in the second sentence when it teaches "administer 5 to 15 mg/day", that language excludes a total dose of 3 mg per day because it does not say "up to". It says the dose *is* 5 to 15 mg/day (my emphasis). Thus a claim to "up to … 5 mg per day" is not supported.

222. In my judgment the dosing in the claim is expressly disclosed in the second sentence which begins with the word "Preferably", when read in context. The context is that the first sentence discloses administering the drug with any total daily dose up to 20 mg per day. The lower limit is 1 mg because that is the smallest tablet.

223. The preferences being referred to in the second sentence are alternatives to the "total dose of 20 mg per day" referred to in the previous first sentence. In other words, the skilled person would understand the document to mean that the dosage forms could be administered up to a total dose of 20 mg per day or preferably that that total dose is 5 to 20 mg per day, or more preferably it is 5 to 15 mg per day. The most preferable approach is to administer a total dose of 10 mg per day by using a 10 mg dosage form. Thus a total daily dose of 5mg is disclosed and so is the idea of dosing up to a total of 20mg/day. A skilled reader is not given new information when they are told (by claim 1 as granted) to use dosing up to a maximum total dose of 5mg per day.

224. The claimants I think also argued that the first sentence did not disclose any daily dose other than 20 mg/day. That is not the right way of reading the sentence since such a daily dose would mean that the reference to a 1 mg tablet was limited to the idea of giving twenty 1 mg tablets together. The sentence expressly refers to giving "one or more" 1 to 20 mg tablets. Giving one 1 mg tablet does not give a 20 mg dose.

225. Turning to the dose in a dosage form, the argument boils down to whether the claimed sub-range of 1-5mg dose in a dosage form is disclosed by the broad range of 1 - 20mg in the first sentence coupled with the other statements in the priority document. In my judgment it is. The skilled reader would see that the idea of a dosage form which contained any dose from 1 mg to 20 mg is expressly contemplated. The document also contemplates administering one or more dosage forms up to a total dose of 20 mg per day in the first sentence of the quoted passage. Therefore the idea that the total dose in a day may be given by delivering multiple tablets is expressed. The document also contemplates administering less than 20 mg to a patient in a day, in the second sentence. For any dose less than 20 mg per day, the dosage form necessarily will have to have less than 20 mg in it too. The idea of administering a total dose of 5 mg per day is also expressly described as the bottom of two sub-ranges in the second sentence. Clearly to administer 5 mg per day would require one tablet with a 5 mg dose, or two tablets with 2.5 mg or even five 1

mg tablets (etc.) as the skilled reader would understand. The reader is therefore necessarily being presented with the idea of using dosage forms containing between 1 and 5mg each. So the sub-range is disclosed in the priority document.

226. I recognise that one could argue that since delivering a total dose of 5 mg in a day could be achieved with five 1 mg tablets, a single 5 mg dosage form is not inevitable on this reasoning. The answer to that is that the sentence bridging the pages refers to "one or more" dosage form being administered up to the total dose and so the idea of using one tablet to administer any total dose expressly identified is disclosed. Claim 8 of the priority document also mentions a 5 mg dose per tablet.

227. However what is not expressly disclosed in the priority document is a dosage form containing 2.5 mg drug either directly as a dose in a tablet or indirectly as a total dose in a day. Although Lilly's closing skeleton arguments referred to the 2.5mg dosage form in a heading (paragraph 356) I did not detect any argument to support claims 2 or 12. I find that claim 2 and claim 12 lack priority.

Priority – overall

228. I have taken the points separately but it is necessary to consider the matter as a whole and also to consider the impact of my conclusion that Compound 5 is not disclosed as tadalafil.

229. The combination of tadalafil as one of the drugs to which the teaching relates, the content of the dosage forms (1-5mg drug) and the maximum total dose of 5 mg per day are disclosed in the priority document. Based on the general teaching, the reader would understand that what is disclosed is that at all the doses described (including 5 mg per day and also up to 20 mg per day) the drug will be an efficacious treatment for sexual dysfunction, will have minimal side effects (including vision and flushing) and can be administered without significant interactions with nitrates. The fact that the document is focussed on a wider idea of finding selective PDE5 inhibitors defined by the three criteria does not mean that the more particular disclosures relating to tadalafil are absent.

230. That leaves open the issue of enablement, which in this context means plausibility. The issue matters because the priority of the use claim 7 and the purpose limited product claim 10 depend on it. Although there had been arguments about the scope of what was in issue in these proceedings, in my judgment given the complexity of the combinations of issues in this case, it needs to be addressed now that the issues have fallen in the way they have. It is also the case that there was no evidence expressly directed to this point but the evidence from both sides did range over the issues necessary to educate the court in order to deal with it. Lilly's submission in closing (p1330-1331) was that there was no need for Example 5 to relate to tadalafil in order to support these claims. The effects were plausible given what was said about selectivity in the priority document even if Example 5 is not tadalafil. I agree but in order to explain why I will say a brief word about plausibility.

231. In ***Merck v Ono*** [2015] EWHC 2973 (Pat) I considered a submission that *in vivo* data were required to make the invention there plausible (paragraph 135). I did not accept that there was any such principle and concluded at paragraph 139 that:

> "The principle applicable to purpose limited medical use claims must be that the material relied on to establish plausibility must be both sufficiently specific, and have a sufficient breadth of application, to fairly support the claim both in terms of the nature of the agent claimed to have an effect, and in terms of the effect claimed."

232. I maintain that view. The issue of enablement of a use claim (which involves plausibility) is a fact sensitive question. It cannot be summarised as a requirement for *in vivo* data. So the fact the drug tested *in vivo* in patients in Example 5 is not disclosed as tadalafil does not necessarily rule out an enabling disclosure of the use claims.

233. In ***Actavis v Lilly*** [2015] EWHC 3294 (Pat) Henry Carr J considered plausibility and stated his conclusions at paragraphs 173-178. I agree with them. The contrast is between a credible claim and a speculative claim. The EPC does not require that every patent must contain data or experimental proof to support its claims but depending on the facts experiments may be required. Plausibility is not the same thing as a reasonable prospect of success in obviousness. Nevertheless the same factual considerations which bear on plausibility may have a bearing on obviousness.

234. Claims 7 and 10 (and the other use claims) are specific to using tadalafil to treat sexual dysfunction. The priority document makes what is claimed plausible because the document provides data showing that tadalafil (Compound 4) is a PDE5 inhibitor and since, as the skilled reader would know but the document explains anyway, sildenafil works to treat this disease by being a PDE5 inhibitor, the basic effect is plausible. The idea that tadalafil would produce efficacy at the doses claimed with minimal side effects is also plausible because the document expressly discloses the doses, sets out a rationale that this effect is due to being a "selective PDE5 inhibitor" based on the three criteria, and explains that tadalafil is a selective PDE5 inhibitor. The claimants did not suggest that the rationale was not credible. The rationale is also supported by Examples 4 and 5. Although Example 5 is not clearly tadalafil, it nevertheless supports the teaching that a selective PDE5 inhibitor based on the three criteria would have the desired effect. If one compound with the desired property does this then it is credible that another will, albeit no doubt tests will be needed. Example 4 supports the general rationale albeit since it is for 10mg tadalafil rather than a 5 mg dose it cannot directly support the claims. Overall in my judgment the use claims are supported by what is disclosed in the priority document and so all the claims (bar claims 2 and 12) maintain priority.

Added matter - 181

235. The law on added matter is not in dispute. I can deal with it shortly. The correct comparison is between the granted patent and the application as filed.

236. There is no issue about identifying tadalafil in the application both as a chemical entity and as the drug used in the relevant examples. That is clearly and unambiguously disclosed. The argument is about the references to dosage forms of 1-5 mg and administration up to a maximum total dose of 5mg per day. The application contains more examples than the priority document, including examples of dosing up to 100 mg, but nevertheless on page 8 of the application the same text about dosing is present as appears in the priority document at pages 6-7. Nothing in the extra material in the application undermines a conclusion that if, as I have held, the claims are supported by that passage in the priority document then they are also supported by the application. Accordingly there is no added matter in the claims. That includes claims 2 and 12 since, unlike the priority document, the application does expressly disclose a 2.5 mg tablet (e.g. claim 4).

237. I have considered whether the amendments made to generate paragraph [0084] as granted (which is now paragraph [0087] in the B3 specification) involve added matter even if the claims do not. I doubt this is an important point since it could be amended in any event but I concluded in the end it does not. The argument in favour is that effectively implicitly new information is taught in the patent. This is because a dose like 10 mg, which the application expressly characterised as having minimal adverse effects, now could be said implicitly to be characterised as having side effects which are not minimal, but I think that is reading too much into the new paragraph.

Novelty - 181

238. The law on novelty relevant to the 181 patent was not in dispute.

239. Since claim 2 and claim 12 do not have priority, Lilly does not defend their novelty over Anderson and Oren. These two claims are invalid.

240. Stoner is relied on against the claims which maintain priority. The contents of Stoner are only s2(3) (Art 54(3)) prior art against the claims of 181 which are entitled to priority if Stoner itself is entitled to its claimed priority. There are two issues: first is the matter in the Stoner application entitled to its own priority? and second does Stoner anticipate the claims of 181?

241. On the first issue, there is no dispute that to establish priority two things must be established. They can be conveniently called substantive priority and legal priority. The former requires the application of Art 87(1) EPC "same invention" test or in other words is the content of the application relied on supported by matter disclosed in the priority document. The latter requires the legal formalities for a proper claim to priority to be established (see ***Edwards Lifesciences v Cook Biotech***).

242. The issue is legal priority. The problem raises a small point of some general importance. In its form as published Stoner carries on its face a reference to US priority application 60/123,244. There is no dispute that the relevant

matter in the published application satisfies the test for substantive priority considering the contents of the priority document. However the parties do not agree about legal priority.

243. All the court has to go on with respect to legal priority is the published application and the copy of the priority document which has been obtained from the relevant public file. Neither side has sought to call evidence of the result of any investigations into legal priority. Neither side has sought to call evidence of any contact with the company which applied for Stoner, Merck & Co. Inc. nor with the named inventors Elizabeth Stoner or Joanne Waldstreicher both of whose addresses are given as the same address in Rahway, New Jersey, USA as Merck itself. Neither side has asked this court to make an order for disclosure against Merck or to issue letters of request to the US court. I infer neither side has used the US 1782 discovery procedure either.

244. Lilly contends that the burden of proof on invalidity is on the claimants as the applicants for revocation. They have failed to establish a crucial requirement for the invalidity claim over Stoner and so they should lose. Lilly also points out that the claimants used the formal Notice to Admit procedure and asked Lilly to admit Stoner's legal priority. Lilly made no admission and in those circumstances it should be for the claimants to call evidence to prove its case if it wished to do so. It has not and so the claimants should fail. The claimants deny this. They contend that while the legal onus rests with them, the available evidence raises a sufficient case to support legal priority such that the evidential onus has shifted onto the patentee. If the patentee wishes to call evidence to rebut that inference it is free to do so but that has not happened. So legal priority should be established. The claimants submit that the fact that a Notice to Admit was served and answered does not alter this analysis.

245. In principle this point will arise every time s2(3)/Art 54(3) prior art is relied on as long as the prior application's relevance depends on its own claim to priority and in particular when the applicant in whose name the prior application was filed is not a party to the proceedings. That will not be an uncommon occurrence, particularly in the EPO. Nevertheless neither side cited any case in which this question had been considered. I infer that the EPO's approach is just to assume legal priority exists in such a case.

246. The correct general approach must be as follows. Legal priority does need to be established. It is a mandatory requirement for priority. Without it the relevant application is not prior art under s2(3) /Art 54(3). The legal burden of proof lies on the party attacking validity, in this case the claimants. However, if sufficient evidence is available to support an inference that legal priority exists, an evidential burden will have shifted to the patentee (Lilly) to call evidence to rebut that inference.

247. In my judgment the Notice to Admit and Lilly's answers to it do not alter this analysis. Lilly submitted that given the notice from the claimants it was reasonable to expect that the claimants would take on the burden of proving legal priority. I accept that but only in the sense that the legal burden of proof

always did rest on the claimants. Nothing in the Notice could be taken by Lilly to indicate that the claimants were representing that they would call evidence from Merck or the inventors of Stoner or that they would accept an onus to do so. If the material before the court shifts an evidential burden onto Lilly, the Notice and Lilly's response to it do not change anything. Had it wished to do so Lilly could always have sought evidence from Merck or the inventors itself.

248. On the face of the priority document, one can see that the named inventors are Ms Stoner and Ms Waldstreicher. On the face of the Stoner application applicants for all states outside the USA are Merck & Co. Inc. and Ms Waldstreicher. The inventor/applicant for the US only is Ms Stoner. This difference is likely to arise from the US practice whereby patent applications have to be made in the name of the inventor although they can be assigned subsequently to their employer. In Europe the inventor's employer can make an application in its own name.

249. In my judgment the application taken at face value supports an inference that legal priority exists. Stoner is a PCT application. The relevant applications for s2(3)/Art 54(3) would be the designations for a European patent (UK) and a UK national patent. Both are included in this PCT. The applicants for those applications are Merck & Co. Inc. and Ms Waldstreicher. Since Ms Waldstreicher is named as one of the inventors, prima facie her claim to legal priority is strong. Merck's claim to legal priority is likely to be on the basis that they derive title from Ms Stoner. When the applicant is a major international pharmaceutical company, the court is entitled to take notice of the fact that organisations of that kind have professional patent departments, part of whose function is to ensure that these sorts of formalities are complied with correctly. The same would be true if the applicant was professionally represented. The fact that Merck's patent department (whose existence is mentioned on the cover sheet of the priority document) has gone to the trouble of carefully distinguishing between Ms Stoner and Ms Waldstriecher on the face of the PCT supports the inference that someone has taken care about the formalities.

250. Things might be different if Stoner was an application belonging to either side but it is not. In this case each side would encounter the same difficulty if they sought to go behind the face of the documents.

251. Absent evidence to the contrary, there is sufficient evidence to support the inference that legal priority exists. The evidential onus has therefore shifted to Lilly to call evidence to rebut that inference. It has not done so. Therefore I find that Stoner is entitled to priority from its priority document.

252. Before leaving this issue, I will say the following. It would not be right to say that the inference will always be drawn in this way based on the face of an application and priority document, however I would expect the court to be able to draw an inference of this kind from this sort of material in most cases when the application is by a third party. Thus in practice in most cases it should be for the patentee to articulate in a statement of case a positive case why the inference that legal priority is secure should not be drawn if it wishes

to take the point once the relevant prior art has been pleaded. That is no real hardship for a patentee. It does not mean that the investigation has to be done by the patentee, because as counsel for Lilly pointed out the patentee is in no better position than the claimants in this case to carry out the investigation. But it does mean that the issue can be case managed appropriately. Otherwise the costs of patent cases will increase due to unnecessary investigations into legal priority of prior art.

253. I turn to the question whether Stoner deprives the claims of novelty. Stoner is concerned with a combination therapy for treating erectile dysfunction. The combination is of a cGMP PDE specific inhibitor such as a PDE5 inhibitor such as sildenafil or tadalafil (named IC-351 in Stoner) together with an alpha-adrenergic receptor antagonist (such as melanotan-II). The alpha-adrenergic receptor antagonists are centrally acting drugs which have been found to initiate erections in men with psychogenic erectile dysfunction. A very wide range of unit dosage forms are disclosed, ranging from 0.01 to 500 mg of each active ingredient (p14 ln12-17) and a wide range of dosage levels are disclosed from between 0.001 to 50 mg/kg per day. These wide ranges include the unit dosage forms and daily dosages claimed in the claims of 181. Although clearly Stoner discloses a much wider range of drugs than tadalafil, and a much wider range of dosage forms and daily dosages than are claimed in 181, if Stoner was concerned only with monotherapy with a cGMP PDE specific inhibitor then I would find that the claims were anticipated. That would include the use claims. Although there is no data in Stoner to indicate efficacy, Stoner clearly asserts (i.e. discloses) that the inhibitors at those doses are effective. The fact that Mr Muirhead accepted that to find out which doses would work would require a clinical trial is not the issue. The disclosure will be enabling if the assertion is plausible. It is also true that, as Lilly points out, there are no data in Stoner indicating efficacy. Lilly then argues that accordingly the skilled clinician cannot learn anything about tadalafil's efficacy for erectile dysfunction. I do not accept that. Stoner describes the clinical approval given to VIAGRA (sildenafil) and makes the point that tadalafil has the same mode of action. Based on this information tadalafil's efficacy is plausible. It is also true that there is no data showing which particular doses would be effective as monotherapy. However the claimed dosage forms and daily dosages are disclosed and there is no suggestion of a selection invention here. So if Stoner was monotherapy (which it is not) then it would anticipate.

254. However Stoner is not concerned with monotherapy, it teaches the use of a combination of the two kinds of drug. Dr Brock's evidence was that the combination with the centrally acting agents drug made a significant difference. He thought the synergistic therapy discussed in Stoner was problematic and said in cross-examination that "all bets are off". Dr Brock also said that the skilled person reading Stoner would not believe that it disclosed increased efficacy from the combination, that the skilled person would understand that centrally acting agents have a very intolerable side-effect profile and that the combination may actually negate any positive benefit of the peripherally acting PDE5. On the question of dose Dr Brock said that if you look at combination therapy it muddles the situation, because

you do not know if that centrally acting agent is going to modify totally the response you may see from a dose.

255. For Stoner to anticipate, it must be an enabling disclosure of what is claimed. Stoner clearly teaches a combination therapy and while the claims of 181 are wide enough to cover such a combination, the question is whether Stoner amounts to an enabling disclosure of an efficacious combination therapy involving tadalafil at the claimed doses. In my judgment it does not because although it asserts that the various doses are efficacious, Dr Brock's evidence shows that there is no basis for concluding that the particular combination of tadalafil at the relevant doses together with a centrally acting alpha-adrenergic receptor antagonist will have efficacy. There is nothing which makes it credible (plausible) that such a combination will work.

256. I reject the claim for anticipation by Stoner.

Obviousness – 181

257. An invention must involve an inventive step, which means it must not be obvious to a skilled person having regard to the state of the art (s1(1)(b) and s3 of the 1977 Act, Art 56 EPC). The structured approach to the assessment of obviousness was set out by the Court of Appeal in ***Pozzoli v BDMO*** [2007] EWCA Civ 588.

258. The skilled person (team) and the common general knowledge have been identified above. The prior art relied on is Daugan. It discloses the idea of using compounds which are PDE5 inhibitors for the treatment of male erectile dysfunction. The document specifically describes two compounds A and B as "compounds of the invention" in Daugan (p3 ln23-28). Compound A is tadalafil. The IC_{50} against PDE5 is given as 2nM (p17 table 1). Examples of a tablet containing a 50mg dose of the active ingredient are given (e.g. p12). No point on formulation is taken in the argument about obviousness of 181 over Daugan (save for the fact that developing a suitable formulation is one of the tasks which would have to be performed). Daugan discloses that doses of Compounds A and B will generally be in the range of from 0.5 to 800mg daily for the average adult patient (p5 ln3-4).

259. It is convenient to consider the obviousness of dosing tadalafil at 5mg per day using a 5 mg tablet. Claim 7 includes this and is a purpose limited EPC 2000 product claim in which the product is for use in treating sexual dysfunction. For obviousness all the claims stand or fall together with claim 7. Although claim 7 refers to the broader indication "sexual dysfunction" whereas claim 9 refers to male erectile dysfunction, nothing turns on that here.

260. So far, bearing in mind the ***Pozzoli*** framework, I have not mentioned inventive concept nor characterised the step between Daugan and claim 7. What is clear and common ground is that Daugan does not specifically disclose a 5 mg daily dose of tadalafil within the wide range disclosed nor does it specifically disclose that such a dose is an effective treatment for male erectile dysfunction. Both of those are features of claim 7. Nothing turns on the dose in the tablet. At this stage I will not go further because the points on inventive

concept and the proper characterisation of the step relate to fundamental differences between the parties about the correct way to approach obviousness in this case. Often the answer to a problem depends on the question which is asked. That is true in this case and in order to explain it and other wider questions posed by the parties' submissions the arguments need to be examined in more detail. I have not forgotten Lewison LJ's warning about over-elaboration of the obviousness question in ***MedImmune*** but given what has been argued I do not believe it would be right not to explain which points I accept and which I do not and why.

261. The overall shape of the claimants' case is as follows. They submit it would be obvious for a skilled team given Daugan to take tadalafil forward into a routine pre-clinical and clinical trial programme as an oral treatment for male erectile dysfunction at the priority date. That sort of programme would be very costly and time consuming but that does not make it anything other than routine. No inventive effort would be required for the programme to succeed in establishing tadalafil as a safe, tolerable and effective treatment for male erectile dysfunction. In the course of that programme a 5mg daily dose would be one of the doses used in patients. The programme would reveal the invention. It would reveal that a 5 mg daily dose is a safe, tolerable and effective treatment for male erectile dysfunction. So the claim lacks inventive step. Also the claimants contend a 5mg daily dose of tadalafil is obvious on its own merits.

262. At the forefront of their submissions the claimants refer to the ***Finasteride*** case (***Actavis v Merck*** [2008] EWCA Civ 444). This is an important judgment because it decides that a dosing regimen can be a feature which makes a Swiss form use claim (and no doubt an EPC 2000 claim) novel as a matter of law. This is critical for the validity of the claims of 181. Without this the claims would be anticipated by Daugan. However although the Court of Appeal held that such claims could be novel, in the judgment of the Court given by Jacob LJ, paragraphs 31 and 32 warned as follows (my emphasis):

> "31. Accordingly on the basis of *Eisai* alone we would hold that Swiss form claims are allowable where the novelty is conferred by a new dosage regime or other form of administration of a substance.
>
> 32. So holding is far from saying that in general just specifying a new dosage regime in a Swiss form claim can give rise to a valid patent. On the contrary nearly always such dosage regimes will be obvious – it is standard practice to investigate appropriate dosage regimes. Only in an unusual case such as the present (where, see below, treatment for the condition with the substance had ceased to be worth investigating with any dosage regime) could specifying a dosage regime as part of the therapeutic use confer validity on an otherwise invalid claim."

263. The words underlined are not really a statement of law and the claimants do not suggest that they are. They are a firm observation about what the facts usually are given the nature of pharmaceutical development, obviously based on the long experience of Jacob LJ in this field, combined with an observation about how the law is likely to apply to those facts. All the same the claimants are entitled to emphasise this part of the Court of Appeal's judgment.

264. Also at the forefront of the claimants' case in closing (paragraph 1) is the submission that both patents in this case are "an attempt by ICOS/Lilly to extend the practical monopoly they have enjoyed over tadalafil and its use in the treatment of erectile dysfunction". That is because, they contend, any competent team making a pharmaceutical product containing tadalafil would routinely carry out standard dose ranging studies which would lead to the dosing claims of the 181 patent.

265. Counsel for Lilly's submissions met this head on, submitting:

> "… the motive for defending these patents is straightforward. It is to recover in respect of and provide the incentive for the expensive and uncertain research programmes that are entailed in getting a drug to market for the benefit of patients. There is, … far, far more involved in getting a safe and efficacious drug to the patient than just finding the molecule. And in that lengthy and costly process there is every reason to reward the results of that research and development programme."

266. Counsel referred to an earlier passage in ***Finasteride***, at paragraph 29, which includes the following (my emphasis):

> "When Mr Thorley was asked what policy reason there should be for on the one hand allowing Swiss form second medical treatment claims for different diseases but not allowing them for the same disease, the only answer he could devise was that the treatment might cost more. Why, he said, should you have to pay more for a 1mg pill than for an out of patent 5mg pill? The reason is obvious – the 1mg pill has only come about because of expensive unpredictable research. Patented things often cost more. And the reason is because the monopoly has been given as result of the research which led to it. Research into new and better dosage regimes is clearly desirable – and there is simply no policy reason why, if a novel non-obvious regime is invented, there should not be an appropriate patent reward. Such a reward cannot extend to covering the actual treatment but a Swiss form claim which specifies the new, inventive, regime is entirely in accordance with policy."

267. Both side's submissions are too wide to be helpful. The law is that dosing regimes are capable of being patentable subject matter. However, as the Court of Appeal point out in ***Finasteride***, although dosing regimes are capable of being patented, most dosing regimes are in fact obvious. Note that I do not say and neither did the Court of Appeal that most dosing regime *patents* are obvious. That is a different issue altogether. Patents on obviously obvious dosing regimes are unlikely to be applied for at all or, if they are, are unlikely to be granted. They will never come to court (and the same is probably true for many other so called second generation pharmaceutical developments like formulations). This all goes to show that generalising as both sides have done does not help.

268. Counsel for Lilly is right that there is much more to getting a safe and efficacious drug to the patient than just finding the molecule, and he is right that the process is lengthy and costly process, and he is right that it is inherently an uncertain process. However, beguiling though they are, these submissions would lead one to conclude that the products of those sort of research programmes must necessarily be worthy of patents. The Court of Appeal in ***Finasteride*** could see this sort of submission coming as a likely consequence of their judgment and it is this sort of argument which they were taking care to head off in paragraph 32.

269. The application of patent law to pharmaceutical research seeks to strike a balance. When a molecule is discovered and characterised a patent application like Daugan can be filed. It discloses the molecule and discloses (i.e. asserts) that it will be useful to treat a disease. The assertion is usually based on some rationale (PDE5 inhibition for erectile dysfunction) maybe with *in vitro* data. At that stage the scientists do not know that the particular drug will be safe and effective but they have rational reasons for thinking/hoping that it will. The compound is new and can be claimed as such but in a normal case that claim will only involve an inventive step based on its ability to treat the disease. A new molecule with no function is not an invention. The patent may contain a Swiss style use claim to using the molecule to treat the disease. For either claim the patent does not have to contain data proving it actually does work in patients as a safe and effective medicine. The patent system in general is designed to reward and create incentives for inventions. The patent system as it applies to medicines is calibrated to allow the inventors to file their application early so that they can invest in the costly and uncertain clinical research programmes of the kind counsel for Lilly is referring to. A patent like Daugan (assuming it is granted) would give the inventors a 20 year monopoly which will cover the period during which that clinical research is done and regulatory data gathered, all at enormous cost, and still leave time at the end to sell the successful drug and earn enough money to create the necessary incentive. The income has to pay for research not only into the successful drugs but also the unsuccessful drugs. The system of Supplementary Protection Certificates allows for a term of such a patent to be extended if the drug did not get a marketing authorisation within a certain period in order to try and ensure that the incentive still exists. There is an SPC for tadalafil. Whether it is based on a patent derived from Daugan or another similar patent is not relevant.

270. The problem with Lilly's logic is that taken at the level at which it is pitched it would make a claim to the use of tadalafil to treat erectile dysfunction using any daily dose non-obvious over Daugan, or at least any dose other than 50 mg. That is because it is undeniable that to find out if Daugan's assertions are true would require the very same costly uncertain research programme, a programme with numerous steps from pre-clinical to multi-phase clinical studies and beyond. For all the skilled person knows reading Daugan, a 50mg tablet given as a daily single dose for erectile dysfunction actually might not work. It may turn out not to be safe and effective for all kinds of reasons: dose, bioavailability, side effects etc. Daugan asserts it will work but the skilled team would not take Daugan's word for it. There is no clinical data in Daugan, no doubt for the reasons I have already explained about how patent law is calibrated. However the inventors of a drug cannot get an early patent on that drug based on its likely therapeutic properties but without clinical data in the patent because the law permits that in order to allow the clinical trials to be funded, and then get another later patent covering in effect the same subject matter simply based on the results of those very clinical trials predicted in the first patent.

271. Lilly contends that the claimants' case is one of "obvious to try" and that this can only lead to invalidity if the skilled person has a fair prospect of success. Lilly contends that all that can be said over Daugan is that one might embark on a clinical research programme hoping to succeed, but that is not enough. It cannot be said (says Lilly) that considering a skilled team at the start of the project and given Daugan, that this team would think it was obvious to try 5mg/day of tadalafil with any prospect that it would work. Even if the drug turns out to be safe and effective at a dose like 50 mg (and you never can say until you test it) Lilly argues you cannot say that a low dose like 5 mg would be likely to work. Lilly developed this argument further near the end of the closing speeches and submitted that for the claim to be invalid, what would have to be obvious to a skilled team is not just that a 5mg/day dose would work in the sense of being safe and effective but that it would have the particular beneficial and surprising properties described in the patent of efficacy coupled with minimal PDE5 related side effects. The point was illustrated by reference to the EPO's problem/solution approach applied to the facts of this case.

272. This approach is nearer the mark but it is not quite right either. In the end the test for obviousness is "a single and relatively simple question of fact" (***MedImmune*** Paragraph 94) and "whether a route is obvious to try is only one of many considerations which it may be appropriate for the court to take into account" (***MedImmune*** Paragraph 92). This way of advancing Lilly's case avoids facing up to a key part of the claimants argument which is relied on, leaving to one side the claimants' case that 5mg is directly obvious anyway. This is the Claimants submission that while you may not have had any particular reason *a priori* to think 5mg would or would not work, it was obvious that assuming the drug works at all, as Daugan teaches, there would be a dose level which is the lowest dose level at which it works, i.e. the minimum effective dose. The claimants say that finding out what that dose happens to be for a given drug requires no invention. Moreover, the claimants

submit, the fact that the minimum effective dose (5mg or less) happens to have a particularly beneficial side effect profile is simply a bonus; it cannot turn that 5 mg dose into an invention. 5mg is the minimum effective dose by any other name.

273. In my judgment the claimants are correct in two respects. First, if it is obvious always to seek the lowest effective dose and if finding that that dose is 5mg/day or less does not involve an inventive step, then the fact that the skilled team could not have said at the start that 5mg/day would be effective does not turn 5mg/day into an invention. Second, if the first point is true, then the fact that 5mg happens to have a surprising beneficial property (low PDE related side effects) which would not have been predicted, does not turn it into an invention either. This first point shows one has to take care with a formulation of the legal question which just asks what the prospects of success of 5mg are over Daugan, and the second point shows that care is needed with a legal question which brings in the surprising beneficial properties of the 5mg dose described in the patent. The properties may turn out to be a bonus.

274. Lilly also referred to the judgment of Henry Carr J in the ***Atomoxetine*** case (***Actavis v Eli Lilly*** [2015] EWHC 3294 (Pat)) at paragraph 177 which explained why "obvious to try" alone without a fair expectation of success would provide insufficient incentive for research and development in pharmaceuticals and biotechnology. I agree. However, like so many other statements relied on by each side in this case, one needs to take care with applying wide statements like this out of the context in which they are made.

275. Lilly submitted that assistance could be found in ***Gedeon Richter v Bayer Schering*** [2011] EWHC 583 (Pat) in which Floyd J (as he then was) had to consider how "obvious to try" arguments fit in a multi-step pharmaceutical development similar context to the one in this case. The relevant passage is as follows:

> "113. Where, therefore, the evidence reveals that to arrive at the invention, the skilled person has to embark on an experiment or series of experiments where there was no fair expectation of success, the conclusion will generally be that the invention was not obvious. Mr Thorley submitted that one had to distinguish between experiments which were conducted in order to make an informed decision as to what to do, and experiments which are conducted only because it is believed that they will produce the desired end result. The former type could be obvious experiments to do, notwithstanding that they were performed without any prior knowledge of the result, or whether the result would predict a successful outcome of the whole project. There was an independent motive for driving the project forward, namely to find out whether a solution to the problem was possible.

> 114. I think that the guiding principle must be that one has to look at each putative step which the skilled person is required to take and decide whether it was obvious. Even then one has to step back and ask an overall question as to whether the step by step analysis, performed after the event, may not in fact prove to be unrealistic or driven by hindsight. Thus to return for a moment to the facts of this case, both sides are agreed that there is nothing *per se* inventive in embarking on *in vitro* pre-formulation testing to determine the physico-chemical characteristics of the API. Such tests would be performed in ignorance of the results of the testing and in ignorance of whether any particular formulation strategy would have a fair expectation of success. But they would nevertheless be an obvious thing to do. They are obvious because the evidence shows that the skilled person would do them anyway, as part of his routine work.
>
> 115. How one would proceed after purely routine steps have been performed may involve more in the way of a value judgment. The mere fact that further steps can be characterised as being performed in order to make an informed decision cannot prevent those steps from contributing to a finding of inventiveness."

276. I respectfully agree. This passage explains that some experiments undertaken without a particular expectation as to the result, are obvious. Others of course are not and in the end, once one has analysed each step individually it is still necessary to stand back and look overall.

277. At this stage I should to refer to ***Teva v Leo*** [2015] EWCA Civ 779 which concerned the formulation of a drug combination. The case is important for emphasising two things, one is that the skilled team, albeit a notional person, should reflect the qualities of real skilled people and the other is about the standard of what amounts to a fair expectation of success in the context of "obvious to try". Merely including something in a research programme is not enough.

278. Having reviewed this material, in my judgment the following points are the important ones in the context of this action:

279. Patent law provides a clear answer to the rhetorical policy question posed by the claimants of whether a pharmaceutical originator is entitled to extend the practical monopoly they have enjoyed over a drug and its use in the treatment of a disease by obtaining a second patent. The answer is that the second patent must involve an inventive step (and otherwise comply with the law) and that the existence of an inventive step is a question of fact which is determined by the detailed technical arguments and evidence and the particular facts and circumstances. Wide generalisations do not assist either way. Patents exist to

provide incentives for costly and uncertain research but not all costly and uncertain research will lead to patentable inventions.

280. When the invention derives from clinical and pre-clinical research it may be necessary to consider a stepwise series of tests which a skilled team might undertake. For an invention to be obvious it is necessary but not sufficient for all the individual steps to be obvious. Even if the steps all seem obvious it is still necessary to stand back and look at the facts as a whole because obviousness is ultimately a single question of fact. The risk of hindsight is significant when one is looking at a step by step analysis (***Technograph***) but not all step by step analysis is inappropriate. The skilled team's views about the likely prospects of success must always be taken into account both step by step and overall.

281. Pharmaceutical development work involves a number of rounds of routine testing which are costly and have an uncertain outcome. A good example is routine pre-clinical testing. A skilled team will carry out routine testing of that kind without any expectation as to what any particular result will be. That lack of expectation does not turn the results of truly routine testing into an invention.

282. The reason phase I, phase IIa and IIb, and phase III studies are carried out is because they have uncertain outcomes. But they are routine tests and the fact their outcome is uncertain does not on its own turn their results into an invention. The fact one cannot say before pre-clinical and phase I or IIa tests have been performed what particular doses would be tested in a phase IIb dose ranging study does not by itself make those doses inventive if some or all of them are found to work.

283. At each stage the skilled team will make value judgments about how to proceed based on whatever results are obtained. The fact the results are not predictable from the outset of the entire project does not necessarily make these decisions indicative of invention. An obvious goal is not turned into an invention by the existence of an unexpected bonus effect (***Hallen v Brabantia*** [1991] RPC 195 at 216). On the other hand, the existence of surprising or unexpected properties can be indicative of an inventive step (***Schering-Plough v Norbrook*** [2006] RPC 18 at para 34). If the case turns on whether a particular test is "obvious to try", which it may do especially when a skilled team is having to make value judgments about what to do next, then the skilled team's views about the likely prospects of success will be critical (***Teva v Leo***). A fair prospect of success will be required for that step to be obvious.

284. In the end the programme has to be considered as a whole. Even steps which are individually obvious in themselves need to be taken into account in deciding the overall question (***Gedeon Richter*** paragraph 115).

285. The following statement of Kitchin J made in ***Generics v Lundbeck*** [2007] RPC 32 was approved by Lord Hoffmann in the House of Lords in ***Conor v Angiotech*** [2008] UKHL 49:

> "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."

286. Particularly when considering obviousness as a whole, this statement is significant and useful. It is significant because it does not reduce obviousness down to a single factor. It is useful because it highlights in a non-limiting way some factors which commonly arise which may have a bearing on obviousness. The factors mentioned are motive, multiple avenues, the effort involved and expectation of success. Other factors which I believe can be relevant are the occurrence of unexpected and even surprising results, and also the need for and nature of any value judgments which have to be made along the way.

Obviousness – the facts

287. I start with Daugan. Dr Brock's evidence was that he did not believe Daugan alone would have given the skilled team sufficient impetus to develop tadalafil. Mr Muirhead's evidence was to the contrary. He thought a skilled team would be interested in developing the compounds in Daugan for erectile dysfunction. I find it would be entirely obvious for a skilled team given Daugan to set out taking tadalafil forward into a routine pre-clinical and clinical trial programme as an oral treatment for male erectile dysfunction at the priority date. The statements in Daugan are quite sufficient to make it obvious to do this but the huge success of sildenafil, an oral PDE5 inhibitor, makes it very obvious. Tadalafil would be an attractive potential second in class medicine to develop. Daugan teaches that tadalafil has a promising IC_{50} vs PDE5. It is more potent than sildenafil (with an IC_{50} of about 3 or 3.9 nM). The skilled team would understand the limitation of *in vitro* IC_{50} data and would know that there could be all sorts of factors such as bioavailabilty and tissue compartmentalisation which might limit its clinical utility but that would not deter the team from embarking on such a programme. The fact that tadalafil is one of two compounds singled out in Daugan is not significant either. Neither would the skilled team be deterred by the thought that the holders of Daugan, Glaxo, do not by 1999 appear to have taken tadalafil forward. There could be any number of reasons why that might be so.

288. Routine pre-clinical studies would be done first. They would be undertaken with the firm expectation that they would produce useful data and a reasonable expectation that tadalafil would turn out to be a viable drug. We know those tests would produce favourable results given what we know now about tadalafil. The skilled team would then conduct routine Phase I safety studies in healthy volunteers. A wide range of doses would be tested and the maximum tolerated dose would be established. Repeated daily doses would be tested. This is all routine. Given the positive pre-clinical data, the Phase I studies would be undertaken with a reasonable expectation that tadalafil would

prove to be a safe drug. Again we know that overall those tests would produce favourable results given what we know now about tadalafil.

289. So far tadalafil has not been tested in patients. It is a convenient point to pause and consider what the skilled team would know at this stage. The team would have acquired a substantial body of information about tadalafil's properties. Some key points which have a bearing on this case are set out below. In reaching these conclusions I have resolved certain less significant issues of fact:

i) The phase I studies would show that the maximum tolerated doses for tadalafil would be 500mg in a single dose and 100mg daily dosing.

ii) The routine testing so far would have shown that tadalafil has a higher IC_{50} against PDE6 than sildenafil. That is an indication to the skilled team that tadalafil may have fewer visual disturbance side effects than sildenafil.

iii) Although the potency (IC_{50}) for tadalafil against PDE5 is reported in Daugan as 2 nM, the skilled team would measure it themselves. They might get a value of between about 2 to 2.5 nM (2.5 nM is the value reported in the 181 patent).

iv) The routine testing would include pharmacokinetics and this would have revealed that tadalafil has a half-life of 17.5 hours, which is much longer than sildenafil (4 hrs). The claimants say this would indicate that chronic daily dosing should be tried. I will consider that below.

v) Another pharmacokinetic parameter which would be identified is the mean accumulation ratio which would be between 1.59 and 1.96 with the higher ratio at lower doses (10mg).

vi) The molecular weight of tadalafil would be known (not by testing). The claimants submit that this would demonstrate that the molecular weights of tadalafil and sildenafil have a ratio of about 5:4. The ratio is not in dispute but this point is relevant to a free standing issue about the obviousness of a 5mg dose which I will consider below.

290. After the phase I tests and based on their results the skilled team would design and undertake a "go no-go" phase IIa study of a single dose of tadalafil in a relatively small group of patients. The dose which would be selected by the team would be 50mg. That was common ground between Mr Muirhead and Dr Brock. Dr Saoud's view was that this study would use 100mg if it was on demand and 50mg if it was for daily dosing. I find that the test at this stage would be on demand because sildenafil was approved for on demand use. As for the dose I find that 50mg would be adopted. Dr Brock's evidence on this was summarised in paragraph 6.20 of his first report:

> "Taking [*the pharmacokinetic data*] into account, the skilled clinician would have counselled the skilled team that a 50mg dose would be the best targeted starting

> dose to assess safety, tolerability and efficacy. The skilled clinician would discount the 100mg, due to its unfavourable side effect profile (100% occurrences of musculoskeletal pain and myalgia are not clinically acceptable). The skilled clinician would not select a dose as low as 10 mg because as compared to the 10 mg doses the 50mg dose demonstrated significantly higher drug concentrations, making efficacy more likely. Also, based on this study, the 50mg dose appears to have an equivalent (and in some cases more favourable) side effect profile than the 10mg dose."

291. I accept that evidence.

292. Given the positive pre-clinical and Phase I results and success of sildenafil as an oral PDE5 treatment for erectile dysfunction, the skilled team would embark on this Phase IIa study with a reasonable expectation that the drug would be safe, tolerable and effective at this dose. Given the common general knowledge of sildenafil and how its efficacy could be measured, efficacy in the phase II studies would be measured using questions 3 and 4 of the IIEF questionnaire.

293. We know that such a Phase IIa study would produce favourable results for efficacy and safety given what we know now about tadalafil. The decision would be to "go". The next step would be to conduct routine Phase IIb dose ranging studies in larger groups of patients. In order to do that a range of doses has to be selected in order to establish the dose response. It was common ground that doses in a first dose ranging study would include 25 mg, 50 mg and 100mg. There was a dispute about whether that first study would have only these three doses (Lilly's case) or would include 10 mg and also 5 mg (the claimants' case).

294. Dr Brock maintained that the doses which would be chosen would be 25 mg, 50 mg and 100mg. Dr Saoud's view was the same (subject to a point about 5mg which I will address below).

295. In his first report para 6.20 and footnote 24 Mr Muirhead's opinion was that 5mg and 10 mg would be included because the lowest marketed dose for sildenafil was 25 mg which the skilled person would estimate as the minimal effective dose for sildenafil, tadalafil had potentially a 2-fold greater potency than sildenafil and this would lead the skilled person to include doses of tadalafil 3-5 times lower than the 25 mg sildenafil dose. Dr Saoud did not agree with this logic and gave his reasons in his second report. The simple point was that the difference in potency of about 2 fold did not justify a 3-5 fold reduction in dose. The skilled team's view of the potency (IC_{50}) for tadalafil against PDE5 could be 2 nM or 2.5 nM. The reported potencies for sildenafil are 3 nM or 3.9 nM (the team would measure it themselves). Based on this the difference in potency ranges from nearly 2 to 1.2.

296. In cross-examination when the 2 fold difference was put to him Mr Muirhead made no serious attempt to justify including a 5 mg dose. He said he could

have lived with 10, 25, 50 and 100 but really his evidence was focussed on a different point, namely that if 25, 50 and 100 were tested the results would lead a skilled team to test lower doses. I will address that point below. I thought Mr Muirhead was straining to find reasons to include a dose as low as 5 mg at this stage.

297. In cross-examination counsel for the claimants put a different point to Dr Saoud about why a 5mg dose was obvious based on a thought process starting at the marketed 25 mg dose of sildenafil. I will call this the "three factors point". It is convenient to deal with it at this stage. Counsel made it clear (T5/642/3-14) that it was not put as the reasoning for choosing a dose in a Phase II study but on a wider basis.

298. The logic of the three factors point works this way. The ratio of molecular weights means that a 25mg mass of sildenafil has the same number of molecules as about a 20 mg mass of tadalafil, which is true. Then assuming that tadalafil has roughly double the potency of sildenafil, you get the same inhibitory effect with half the number of molecules of tadalafil as sildenafil, so that takes you to 10mg tadalafil. Then assuming chronic daily dosing, one can consider the accumulation ratio for tadalafil which for 10mg dose is 1.96 (i.e. about 2) and so on daily dosing you get to the conclusion that a 5mg daily dose of tadalafil is equivalent to a 25 mg dose of sildenafil. Mr Muirhead did not advance this three factors theory in evidence so the only evidence for it is Dr Saoud answers in his oral evidence. The claimants' closing submissions set out a passage of transcript at T5/637/6 – 640/3. Dr Saoud's broadly accepted the logic, using words like "rough and ready" and his answer at the end of this passage to the question about equivalence was "using this kind of exercise, yes". However stopping the quotation at p640/3 gives a wrong impression of Dr Saoud's evidence. In his very next answer and what followed, Dr Saoud explained that a skilled person would understand that the rough and ready effect of those three factors would indeed be as discussed but his firm view was that the skilled person would not take that approach. Moreover when it was suggested that the skilled person only had those three factors to go on, Dr Saoud agreed that they were obvious factors but disagreed that they were the only ones. He said there were many other factors, mentioning properties of sildenafil such as concentration, Cmax and bioavailability and the fact that bioavailabilty of tadalafil is unknown. Of the three factors point overall he said:

> "So a paper exercise, that is absolutely fine and dandy,
> but that is not how it goes in real life."
>
> [T5/640/25-641/3]

299. The cross-examination continued. Counsel put and Dr Saoud accepted that the effect of the various other factors could tend either to increase or decrease the result. Then at T5/643/4-14 the following exchange occurred which related to the three factors just identified. The claimants rely on it for the submission that "Dr Saoud also agreed that the skilled clinical pharmacologist would certainly predict that something below 20 mg would be efficacious" (closing paragraph 199). The passage is:

> "Q. And so what I am suggesting to you, these three factors that the skilled person would positively know about would lead the skilled person to know that there may be other factors that could go one way or the other, but as a starting point on your approach a skilled person without any efficacy data at all would believe that rough and ready the 25 mg of sildenafil should equate to about a 5 mg of tadalafil.
>
> A. Using these criteria only as a paper exercise, yes.
>
> Q. One thing we can say for sure is that he would certainly predict doses below 20 mg would be efficacious. Yes?
>
> A. Yes."

300. Having heard Dr Saoud's cross-examination as a whole, taking that last question and answer in isolation risks giving a wrong impression. Dr Saoud had explained that he thought the three factor point was a paper exercise, that his opinion was that the skilled person would not take that approach, and that this was not real life. However, he did understand the three factor point and he properly accepted, as he had before, that on the premise one was going to use that approach and therefore only take into account those factors, then the conclusion would be the one proposed by the cross-examiner.

301. Dr Saoud was asked about this in re-examination. The question put was a leading one and I doubt the answer counsel was after would have assisted but, in my judgment to his credit, Dr Saoud maintained his evidence, as he had given it in cross-examination, in a clear answer: based on the three factors the conclusion advanced certainly follows. Counsel had another go at asking a leading question along similar lines but I stopped him.

302. The claimants submit that in this re-examination Dr Saoud confirmed that the skilled person *would* (my emphasis) come to the conclusion that doses below 20 mg would be efficacious from just the three factors yet without knowing other factors such as bioavailability. I reject that submission. Dr Saoud made clear in cross-examination that he did not accept that this was anything other than a paper exercise. It was not real life.

303. I find that the three factor point does not represent the thinking of the skilled person in any circumstances relevant to the questions I have to decide.

304. I will also add this. One of the vices of raising a point like this in cross-examination when it is not foreshadowed in the expert evidence is that it can become a test of how quickly people can think. That is not helpful. As I have been considering this issue it occurs to me that there may be an inconsistency built into it. To deploy the third factor the skilled person needs to have found out the accumulation factor for tadalafil, i.e. to have acquired pharmacokinetic data. But the questions sought to exclude knowledge of other bioavailability and pharmacokinetic data as unknown factors which could go either way.

Since I have not accepted the point in any event I do not have to decide this issue.

305. So, rejecting the three factors point I return to the question of which doses would be selected in the dose ranging study. A further small but relevant point is about the number of arms in a dose ranging study. Mr Muirhead accepted that for many drugs two or three doses would be studied although four was not unheard of in a dose ranging study.

306. I find that the tadalafil doses which would be tested in this first phase IIb dose ranging study would be and would only be 25mg, 50mg and 100mg. The test would be of on demand dosing.

307. The skilled team's expectations about this study would be that they would hope it would show a dose response relationship. They would know there was efficacy at 50mg and hope that to the extent any effect was seen at 25mg, it would be less than at 50 mg. They would hope that the effect at 100mg would be higher than at 50mg. That is why those three doses would be chosen for dose ranging. However they would not necessarily expect the effect at the lowest dose (if any) to be large enough to be clinically relevant. That is a different issue. I will address the minimum effective dose issue below.

308. Turning to side effects, Lilly submitted that the skilled team's expectations about the likely side effects of tadalafil would be that they would show the same essential relationship to dose as would be seen with efficacy. Lilly relied on Dr Brock who stated in his report that the evidence was that the desirable therapeutic effect of a PDE5 inhibitor is a consequence of the vasodilation and smooth muscle relaxation, which is also the cause of the commonly-occurring side effects. He said therefore that it was thought that whilst lowering the dose would decrease the incidence of side effects, so would it reduce efficacy because they have the same root causes.

309. The claimants pointed out that as a matter of common general knowledge the skilled team knows that in principle the dose/response curve for a side effect of a given drug need not be the same as for the clinical effect for that drug. So for example, for an orally administered drug like sildenafil, to function the drug has to reach a certain level in the systemic circulation and then diffuse into the penis tissue. It is the level in the penis not the level in the blood stream which has the desired effect. However, the facial flushing side effect may depend on the level of the drug in blood vessels in the face. A different drug may have a different relative tendency to partition and diffuse into these two different tissues.

310. Dr Brock accepted this as a matter of principle but emphasised that the experience of sildenafil was that there were important side effects which were related to its mode of action as a PDE5 inhibitor and that experience was that the side effects and efficacy were "very much linked". He referred to facial flushing and in a colourful passage of testimony Dr Brock explained that he would often tell his patients to regard the onset of the facial flushing side effect as an indication that sildenafil was at an optimum concentration in their system for it to work.

311. This is an issue which involves both clinical pharmacology and direct clinical experience. Dr Brock was the only clinician to give evidence and I accept his evidence.

312. A significant point in the case arises at this stage because the results of this phase IIb study would not be what the skilled team expected. The claimants referred to the results of a real double blind placebo controlled phase II study of tadalafil called LVBG which was carried out at 19 centres internationally in about 300 patients with mild to moderate erectile dysfunction. It was a daily dosing study testing four doses 10, 25, 50 and 100mg. The results were that there was no difference in efficacy end point between all four doses demonstrating an apparent therapeutic plateau. The most common side effects were headache, back pain and myalgia and these side effects did show a dose response. 10 mg and 25 mg tadalafil were well tolerated and all doses up to 100mg were "generally" well tolerated. Although this is a daily dosing study and on demand will be different, there was no suggestion that essentially the same sort of results would follow.

313. I find that the results for the 25, 50 and 100mg on demand Phase IIb study would be essentially the same as the results described above for LVBG.

314. The claimant's case was that the obvious thing to do at this stage was to conduct a further dose ranging study or studies to investigate lower doses and determine the minimum effective dose. In support they relied on four main points:

315. First Mr Muirhead's evidence. His evidence about what the skilled team would do from here was very clear. His firm opinion was that it would be obvious for the skilled team to carry out further dose ranging studies in these circumstances, to investigate lower doses and to determine the minimum effective dose. He was unshaken in cross-examination on this point. He said "the data will take you where you need to go". His evidence was usually framed on the idea of a Phase IIb study which included a 10 mg arm but the logic is no different.

316. Second, the claimants relied on the fact that a minimum effective dose was a concept within the common general knowledge and as part of that the skilled team would know that it was something the regulators would ask to be investigated.

317. Third the claimants relied on Dr Saoud's evidence in cross-examination. In the context of considering the implications of study LVBG it was put to him that it was a "no brainer" to go to a lower dose because the doses were at the top plateau for efficacy and that the team would know that going lower would reduce the side effects. He agreed. There was a point about the patient population but I was not convinced that that made any difference.

318. Fourth the claimants relied on what happened in practice in the case of tadalafil. This is a convenient stage to explain the extent to which I have decided I can place weight on what happened in practice including what Glaxo may or may not have done or thought and what ICOS and Lilly did. I will rely

on the factual evidence of the outcomes of particular studies. That does not cause difficulty. I have no proper evidence about Glaxo and I will not place weight on that. I can place weight on the fact that the tadalafil project did involve tests in which doses were identified as a minimum effective dose purely for the fact (which I have found already) that the skilled team understood the concept. However, as Lilly points out, different doses were identified as the minimum effective dose in different studies. I do not have sufficient evidence about this to place any further weight on it either way. I can note that the regulators did ask for the minimum effective dose to be investigated but since the regulators were presented with the data the developers of tadalafil actually produced, that act by the regulator is only really relevant to the questions I have to decide if that data presented to the regulator in real life was the same as the data which a skilled team would generate. That is almost certainly not the case. The evidence shows that the real development project for tadalafil involved quite an array of clinical trials of various kinds. It is impossible and unproductive to embark on trying to say whether all that was obvious or not.

319. Lilly relied on factual evidence from Dr Pullman and Dr Saoud in support of non-obviousness. I appreciate that the skilled team should reflect reality (***Teva v Leo***) but I am not convinced it is possible or productive to place weight on that evidence. There was evidence about a "hunch" of Dr Pullman's about possible efficacy at very low doses which Dr Saoud explained Dr Pullman had had before seeing the results of an ICOS study at that sort of low dose but to decide if it is relevant I would need to analyse whether Dr Pullman was in the same position as the notional skilled person armed only with the common general knowledge and the results of obvious tests. I am in no position to do that. Moreover the team of people working on the project was large and included many individuals who did not give evidence but were involved in the relevant decisions including (taking the names from Lilly's closing) Steve Whitaker, Ken Ferguson, Gary Wilcox, Tom St. John, Jeff Hesselberg, Albert Yu and a newly appointed Project Manager from Lilly, whose first name Dr Saoud could not recall (Mr Davenport). To place weight on what one or two individuals in such a large team thought or did would require consideration of the others, which cannot be done.

320. I turn to Lilly's case against the claimants' submission that the skilled team would investigate lower doses at this stage. Lilly relied on the following:

321. First Lilly submitted that Mr Muirhead's evidence inflated the importance of the minimal effective dose, drawing a contrast with what Lilly did on tadalafil and what Pfizer did on sildenafil. Mr Muirhead had worked on sildenafil at Pfizer. He explained that what Pfizer defined as the minimum effective dose for sildenafil was between 5 and 25 mg. This bears some explanation. As was common general knowledge, in order to define a minimum effective dose a skilled person knows they need to define what a minimum clinically relevant effect is. Lilly submitted that there was at the priority date no standard definition of what that would be for erectile dysfunction. Measurements of the stiffness of an erection can be made using equipment such as a Rigiscan but there was then no agreed correlation between a particular measured value and

a clinically relevant effect. Low doses of sildenafil had been shown to have statistically significant effects measured in this way but whether those effects were clinically significant is another matter. The IIEF questionnaire allows studies to be done of the patients' views about sexual intercourse with their partners when they have taken the drug but again there was at that time no agreed upon basis on which to say that a particular IIEF score was the minimum clinically relevant score. Mr Muirhead accepted this in cross-examination. Dr Brock maintained that the concept of a minimum effective dose in erectile dysfunction was subjective.

322. Mr Muirhead explained that a judgment has to be made by the skilled team about what level they choose to deem to be the minimum clinically relevant effect and that is what Pfizer's team did. Therefore based on the decision made by Pfizer, any effect of 5 mg sildenafil was below the level deemed to be clinically effective while the effect at 25 mg was above that level. 10 mg had been studied too and some efficacy had been shown (and published).

323. Pfizer's experience bears out Lilly's point. While the minimum effective dose was a concept within the common general knowledge in general terms, as applied to erectile dysfunction the skilled team would be well aware that there was no defined standard for minimal efficacy. The claimants submitted this amounted to teams merely making slightly different judgment calls. I do not accept that the point can be minimised in that way. The team would know that to characterise a minimum effective dose would require a value judgment. Different real groups would deem different levels of efficacy as the minimum clinically relevant effect for erectile dysfunction and the skilled team would know that.

324. Also I find that Pfizer did not actually determine what the minimum effective dose for sildenafil was or even attribute that label to a particular one of the doses they tested. It was just identified as being within a range.

325. Lilly referred to Dr Saoud's evidence that it was not his experience that a minimum effective dose would be sought. He did maintain that opinion but it was not consistent with his acceptance about looking for a lower dose in the light of LVBG.

326. Second, aside from the argument about minimum effective dose, Lilly emphasised the positive nature of the results of the Phase IIb dose ranging study – that they showed that 25, 50 and 100 mg doses of tadalafil were highly efficacious, generally well tolerated and safe. I agree. Lilly submitted that Dr Brock's evidence was that he would go forward with those doses and probably not go lower. That is not exactly what Dr Brock said. His evidence in cross-examination was that he would not necessarily go lower. Part of his thinking was influenced by the fact that at the relevant time in 1999 there was a highly competitive market place, which I do not doubt but cannot be taken too far. I also bear in mind that while the clinician's views are important, dose selection is an issue on which the clinical pharmacologist would take the lead.

327. Weighing all this up, the results of the Phase IIb study would require the team to make value judgments. It is not inevitable that a skilled team would

investigate lower doses given the plateau in the results of the Phase IIb study, because by identifying a dose (at least 25 mg) which is safe, tolerable and effective they have secured the prime objective of the programme, but it is very likely. Such an investigation would not be quite as routine for the skilled team as the work which has gone before but that cannot be taken too far. Multiple dose ranging studies in general terms are something the skilled team would be familiar with as necessary.

328. The team would need to decide upon a level of clinical effect which they were going to take as the minimum clinically relevant effect (in fact this would most likely have been done at an earlier stage).

329. For the purposes of the analysis I will assume a single dose ranging study which includes both 5 mg and 10 mg doses as well as the higher ones. The alternative could be a test with 10mg as the lowest dose, which would show 10mg was still on the plateau, leading to a test including 5mg by the same logic as before.

330. I therefore need to examine what the skilled team's expectations would be.

331. The position on this is clear. The skilled team would regard a 25 mg dose of tadalafil as a marketable dose. It would be safe, tolerable and effective. The skilled team will have defined a minimum clinically relevant effect for their own purposes. I am not satisfied that the team would have any expectation that the minimum effective dose was substantially lower than 25 mg. The team would clearly expect that somewhere below 25 mg there would be a dose of tadalafil which did not work, but that is really the limit of their expectations. The skilled team would hope to see a dose response but even if they expected to see any statistically significant effect at 10 mg, they would have no reasonable expectation that 10 mg tadalafil would produce a clinically relevant effect as they had defined it. In terms of expectations, an entirely feasible outcome would be that the minimum effective dose would to be found to be between 10 and 25mg. Dr Brock's evidence was that he could not predict whether 10 mg had efficacy in the light of Daugan. Although that was expressed at an earlier stage in the exercise, it is germane.

332. Even if the testing is in two further stages, testing 10, 25, 50 and 100mg first, finding the plateau includes 10, and then testing a range down to 5mg, the expectations about the 5mg arm of the test relative to 10 mg would be the same as for 10 mg relative to 25 mg in the previous paragraph. In any case an argument which requires three rounds of dose ranging to arrive at the invention is beginning to look like hindsight.

333. I have already rejected the claimants' arguments about expectations based on scaling down from sildenafil dosing.

334. As for side effects, I find that the skilled team would expect efficacy and PDE5 related side effects to go together, for the same reasons I have already addressed. The fact that side effects showed a dose response in the first dose ranging study whereas efficacy was on the plateau would not lead the team to

expect that there might be a dose below 25mg at which a clinically relevant effect was found with reduced side effects.

335. In other words the skilled team testing a 5mg per day dose of tadalafil (on demand) when carrying out these investigations would not have a reasonable expectation that the drug at this dose would be a useful treatment for erectile dysfunction nor any expectation at all that the drug would produce a clinically relevant effect but with minimal side effects.

336. A skilled team which carried out a dose ranging study including a 5mg dose would discover that this dose was efficacious and had reduced side effects. They would be surprised by this. The team would go ahead to do Phase III studies at 5mg/day and seek clinical approval for a 5mg/day dose of tadalafil.

Daily dosing rather than on demand dosing?

337. In the real tadalafil project, chronic daily dosing of tadalafil was investigated and found to be useful. Tadalafil is approved for daily dosing as well as on demand use. I have kept the issue of daily dosing to one side in order to maintain a degree of clarity. I now need to address it.

338. The claimants' case, supported by Mr Muirhead, was that the relatively long half-life of tadalafil as compared to sildenafil would suggest daily dosing. This half-life would emerge from the preclinical and Phase I studies. So along with the on demand studies, testing of tadalafil would include chronic daily dosing. This has a particular relevance because the accumulation factor of tadalafil at low doses suggests that a lower daily dose would be required for an equivalent effect seen with on demand dosing. Lilly's case on this focussed on the expectations of the skilled team and Dr Brock's evidence that the expectation was that chronic dosing would exacerbate or prolong side effects.

339. In my judgment the half-life of tadalafil, which was not predictable in advance but would be discovered early on, would present the skilled team with a value judgment. It would naturally suggest consideration of chronic daily dosing of tadalafil. However, the team would be well aware that sildenafil was an on demand medicine and was very successful. The evidence was that the average frequency of sexual attempts for married and co-habiting couples was about 7 times per month. Why take a pill every day when the therapeutic effect is only required on those occasions? The skilled team would have a substantial concern about side effects. The fact that sildenafil's side effects such as facial flushing are tolerable by a patient who only takes the tablet on an occasional basis does not mean that such side effects, which were thought to be inherently linked to PDE5 inhibition, would be tolerable chronically.

340. I accept Mr Muirhead's evidence that the skilled team would investigate chronic daily dosing of tadalafil but they would not have a strong expectation that it would lead to a useful drug. It might or it might not. This decision would be made after the Phase I studies. It would lead to a Phase IIa Study with the same 50mg/day dose as I have discussed above. Despite the accumulation point the skilled team would not use a lower dose than 50 mg in that go no-go study for daily dosing.

341. The initial Phase IIb dose ranging study which was for daily dosing would probably include a 10 mg dose as an additional arm owing to the accumulation factor. It would not include a dose lower than 10mg/day. The team would expect to see a dose response but would see the same plateau in efficacy down to 10 mg and dose response for side effects as discussed already. All the reasoning I have considered above would be the same. Assuming the team decided to conduct an investigation into lower doses in a second, daily dosed, dose ranging study including a 5mg/ day dose of tadalafil, they would not have a reasonable expectation that the drug at this dose would be a useful treatment for erectile dysfunction nor any expectation that the drug would produce a clinically relevant effect but with minimal side effects. They would find that it did. They would be surprised.

Considering the programme as a whole and obviousness overall.

342. The clinical programme to develop tadalafil over the prior art has many routine and obvious steps in it. Even though Daugan only exemplifies a 50 mg tablet, I am sure that a 25mg/day dose of tadalafil as a treatment for erectile dysfunction is obvious and involves no inventive step over Daugan for a skilled team in the light of the common general knowledge. That is an example of what the Court of Appeal in ***Finasteride*** were referring to.

343. However in my judgment a 5mg daily dose of tadalafil as a treatment for erectile dysfunction is not obvious over Daugan. That is for the following reasons articulated having regard to the factors I identified above based in part on ***Lundbeck***:

i) In terms of motives to find a solution to the problem the patent addresses, the skilled team would be highly motived by Daugan and the success of sildenafil to investigate tadalafil as a treatment for erectile dysfunction.

ii) As for possible avenues of research, overall tadalafil would be obvious to investigate. In terms of doses however, 5 mg/day is a significantly lower dose than the 50 mg dose exemplified in the Daugan prior art and the marketed doses of sildenafil. It is also significantly lower than the 50 mg dose which would be chosen for the first test of efficacy at Phase IIa. It would not be chosen in the routine first dose ranging study. The team would not have anticipated daily dosing as something to be studied from the outset but once the half-life was discovered it is likely that daily dosing would be included.

iii) In terms of effort, overall the programme would involve very substantial resources of time, money and people but it would be pursued. However, by the time the idea of investigating lower doses presents itself, the team would have established safe, tolerable and effective doses of tadalafil at 25mg on demand and 10 mg for daily dosing. At that stage the impetus to investigate lower doses would be reduced but not eliminated.

iv) Expectations of success can be considered overall and in relation to particular studies. Overall the team would embark on the project with a reasonable expectation of success in establishing tadalafil as a safe, tolerable and effective treatment for tadalafil. However, the claimants failed to prove that efficacy at 5mg tadalafil was predictable or worth considering by the skilled team based on the properties of tadalafil as compared to sildenafil. The team would know that in principle there would be a minimum effective dose for tadalafil but would also know that its definition depends on a value judgment made by the team. In relation to the dose ranging studies, the team would conduct them hoping for a dose response. Following discovery of a plateau starting at 25 mg or 10mg, there would very likely be a subsequent dose ranging study which included 5 mg. The team would include a 5 mg dose in this study hoping to see a dose response but that does not mean they would have a reasonable expectation that 5mg would produce a clinically relevant effect at all nor one with minimal side effects. Assuming a 5 mg /day dose of tadalafil was tested, it would not be tested with a reasonable expectation of success.

v) Considering unexpected or surprising results, the position is as follows. The path to a 5 mg dose requires the discovery of new information such as the half life and the IC_{50} vs PDE6. That information would inevitably be found in any clinical programme. The path includes an important result which is unexpected even if it is not actually surprising, i.e. the plateau in the dose response from 10 to 100 mg. There is also a surprising result: the existence of a useful effect with reduced side effects. The claimed 5mg /day dose has that property.

vi) A number of value judgments would be required of a skilled team in a programme which reaches the claimed invention. One is to define the level of clinical effect to be regarded as relevant. Another is to embark on investigating daily dosing. An important value judgment is what to do when an unexpected plateau in the dose response has been identified at the same time as a marketable dose.

344. I find that claim 7 of 181 involves an inventive step.

Insufficiency - 181

345. Following the admissions by Lilly about Anderson and Oren, the squeeze on insufficiency advanced by the claimants falls away.

Infringement - 181

346. I have held that the claimants would infringe a valid patent if they launched their 2.5 mg and 5mg products with the relevant SmPCs. Ordinarily an injunction would follow but there is a point of principle taken by Actavis and Mylan both as regards relief and the cause of action itself. The question posed by counsel in closing is whether a rival such as a generic pharmaceutical company can seek to clear the way with a revocation action, with a contingent intention to launch a product if the action succeeds, without being held to be

threatening to infringe the patent and thereby be subject to an infringement counterclaim? Actavis and Mylan submit that they can. They argue that applying to revoke a patent with the intention to enter the market if the patent is cleared out the way is not a threat to infringe the patent and so there is no basis for bringing the counterclaim.

347. The point is of some practical significance. Actavis and Mylan submit that counterclaims for infringement result in significant and unjustified added costs. One has to do Product and Process Descriptions and so forth. There are demands for samples. Actavis and Mylan submit there is no just reason why it should be inferred that they threatened to infringe a patent just because they seek to revoke the patent.

348. The submission is that I should find as a matter of fact that no threat to do an act which would infringe has been established and so dismiss the counterclaim.

349. Neither side cited any authority on this and there were no witness statements dealing with it. Actavis and Mylan took the view that the plea about their contingent intentions in their Particulars of Claim, coupled with a statement of truth amounted to admissible evidence on the point. Lilly did not object and I will work on that basis although I doubt it is correct given the combined effect of CPR r32.2 and r32.6(2)(b) (which is why a specific direction is usually sought in the IPEC on this point (IPEC Guide para 2.5(d))).

350. The infringement counterclaims in this case are brought *quia timet*. In the context of a "clearing the way" action like this one the infringement claims always are. In the ***Efavirenz*** case (***Merck Sharp Dohme v Teva*** [2013] EWHC 1958 (Pat)) I heard a trial of a similar *quia timet* action in which the only issue was whether the generic pharmaceutical company was threatening and intending to infringe once the SPC expired. The relevant cases were cited. I reviewed them from paragraph 39 onwards and tried to summarise the law as follows:

> "56. The principle I derive from these authorities is that the question the court is asking in every case is whether, viewed in all the relevant circumstances, there was a sufficiently strong probability that an injunction would be required to prevent the harm to the claimant to justify bringing the proceedings. In adding the word sufficiently to the word strong I do not mean to put a gloss on the words of Chadwick LJ [*in* ***Lloyd v Symonds*** *[1998] EWCA Civ 511*], rather I am seeking to encapsulate the idea that the degree of probability required will vary from case to case depending on all the circumstances but that mere possibilities are never enough. To justify coming to court requires there to be a concrete, strong and tangible risk that an injunction is required in order to do justice in all the circumstances.

> 57. If a defendant really does, at the date of the proceedings, have no intention to do the act then in the majority of cases that will be conclusive of the question whether there was a sufficiently strong probability to justify proceedings. (e.g. ***London Borough of Islington***). However it seems to me that the question is not confined to the defendant's subjective intentions. A defendant's overt acts must be capable of being relevant. To take an extreme case, if a man began taking actual preparatory steps to commit some unlawful act seriously damaging to the claimant and in infringement of the claimant's rights and did so in full view of the claimant and well aware that the claimant could see them, he could hardly complain if the claimant started proceedings and the court decided to grant a final injunction to prevent it. A statement at trial that he had never intended to go through with it would get short shrift.
>
> 58. I bear in mind that intentions are not necessarily simple. A state of mind need not merely be either one thing or another. Also in this case the defendants are corporate entities to whom an intention can only be imputed."

351. Recently in the ***Buprenorphine*** case (***Napp v Dr Reddys*** [2016] 1517 (Pat)) Arnold J was faced with a related question and referred to paragraph 56 of ***Efavirenz***.

352. In ***Efavirenz***, in order to decide if there was a sufficiently strong probability that an injunction would be required to prevent Teva from infringing, I looked first at the objective position without regard to the party's case about their actual intentions, then considered their actual state of mind and then the position overall. I will take the same approach here.

353. Viewed objectively today, the UK market for tadalafil is large and valuable. It is obvious that a generic company would wish to sell tadalafil once the SPC has expired. Actavis and Mylan have applied for and are obtaining marketing authorisations for their generic tadalafil products. That is an expensive and time consuming process. Viewed objectively, it only makes sense if they are planning to sell tadalafil sometime. The 181 patent (and, I will assume, 092) are potential obstacles. Bringing proceedings to revoke them is not proof of an intention to sell but it also supports the inference based primarily on the marketing authorisation.

354. Subjectively, Actavis and Mylan contend their intentions are contingent only. They only intend to sell if they revoke the patents. There is nothing inherently improbable about that being someone's intention and given Lilly's stance I will accept that that is what Actavis and Mylan really think today. However, as I put to counsel, intentions can change. I infer given the international nature of this business that they will have substantial supplies of tadalafil once

the SPC expires. The circumstances in the market might create an opportunity in which launching tadalafil at risk was attractive. The companies will have a marketing authorisation in place. No undertaking was on offer when the counterclaim was brought to abandon the marketing authorisation if they lost the revocation action. A surreptitious launch of generic product can be very attractive and profitable even if it is subsequently stopped by an emergency injunction (c.f. the ***Atorvastatin*** and ***Pregabalin*** litigation).

355. Looking at the position overall, in my judgment there is a sufficiently strong probability that an injunction would be required to prevent Actavis and Mylan from infringing after expiry of the SPC to justify bringing the infringement counterclaim.

356. The flaw in the logic of the question posed by Actavis and Mylan is that the inference on which this *quia timet* infringement action is based does not derive solely or even predominantly from the fact they have sought to clear the way by applying to revoke patents. It derives from the marketing authorisation process. Furthermore, while there is a cost and trouble associated with product and process descriptions, that only arises because there is an issue on infringement. The companies are entitled not to admit infringement, but in that case infringement is in issue and should be sorted out in advance just as much as validity. The logic of clearing the way covers both infringement and validity.

The 092 patent

The skilled person and the common general knowledge – 092

357. The 092 patent is addressed primarily to a formulation scientist member of the same team identified for 181. That person would likely have a degree in pharmacy, or a related discipline, possibly a PhD, and in any event some industrial experience in pharmaceutical formulation. This is not disputed.

358. The team would also include a person with pharmacokinetics expertise and a person with clinical expertise (a clinical pharmacologist and/or a clinician). These members of the team are more relevant to the issues surrounding claims 8, 9 and 19.

Common general knowledge – 092

359. The skilled team for 092 is the same team as for 181 albeit the focus now is on formulation. The team has the same common general knowledge. Set out below are some aspects of the common general knowledge of the skilled formulator member of the team which are more relevant to 092 than to 181.

Dosage forms

360. When using the oral administration route, drug products may be presented in several forms, including solid dosage forms, suspensions or solutions. In general, solid dosage forms involve the compression or encapsulation of a powder consisting of the active pharmaceutical ingredient (APl) and added

excipients. In a suspension the API is suspended as solid particles in a liquid carrier and not dissolved. In a solution the API is dissolved in a solvent.

361. Excipients are pharmacologically inert substances that are added to a formulation to confer a benefit typically by improving the handling and manufacture of a formulation, by acting as a "filler" to bulk the formulation up, or by aiding the disintegration and dissolution of the product. Examples of classes of excipients that may be included in a formulation include diluents, binding agents, disintegrants, lubricants, surfactants and glidants. Some excipients may be multifunctional.

362. Tablets are made in different ways including direct compression, wet granulation and dry granulation. Nothing turns on the differences between these techniques.

Absorption

363. After ingestion, a solid oral dosage form will rapidly enter the stomach from the oesophagus. The human stomach provides an acidic environment (with pH typically varying between 1 and 3.5) and has a thick mucus coating over a mucosal membrane that has not evolved to absorb food (and therefore also not well suited to absorb APIs). Once in the stomach, a solid oral dosage form will begin to disintegrate into larger sub-sections (granules) or smaller sections (particles) within the gastric fluid. Soluble components of the tablet will start to dissolve (before, during and after disintegration, most rapidly after disintegration). Inter-individual variability exists in gastric emptying time. Single non-disintegrating tablets may remain in the stomach for between 0.5 and 4.5 hours (but potentially for much longer than this in the fed state).

364. The small intestine is a less acidic environment than the stomach (with a pH ranging from 5 to 7) and represents the primary absorption site of most orally administered drugs. Once absorbed across the wall of the small intestine and into the portal vein, the drug is transported to the liver where it may undergo some form of metabolism ("first-pass metabolism") The drug will then be distributed by the systemic circulation to various bodily tissues and, over time, will be metabolised and/or excreted from the body via, for example, the urine.

365. Gastrointestinal (GI) motility occurs when wave-like muscle contractions push substances along the GI tract. This process determines a drug product's residence time in the different areas of the GI tract. Food, especially fatty food, slows gastric emptying (and rate of drug absorption), explaining why taking some drugs on an empty stomach speeds absorption. The small intestine has the largest surface area for drug absorption in the GI tract, and its membranes are more permeable than those in the stomach. For these reasons, most drugs are absorbed primarily in the small intestine. Intestinal transit time can influence drug absorption, particularly for drugs that are absorbed by active transport.

Solubility

366. The solubility of an API is defined as the amount of that API capable of dissolving in a specific volume of a given solvent at a known temperature. The material that dissolves in the solvent is referred to as the "solute". Once equilibrium is reached, the solution is said to be "saturated". Solubility measurements can be given by reference to the mass of an API that may dissolve in a given volume of solvent (e.g. milligrams per millilitre). The greater the mass of API that may dissolve in a given volume of solvent, the better its solubility.

367. An API's solubility may be determined by adding an excess quantity of the API to a defined dissolution medium (e.g. water buffered to a specific pH) at a constant temperature. The mixture is then stirred for a suitable time (for example for several hours) until equilibrium has been obtained (and a saturated solution achieved). The undissolved API may then be removed from the saturated solution by filtration. The quantity of API dissolved in the saturated solution can be determined by one of a number of analytical methods, such as high performance liquid chromatography (HPLC). An API may exhibit different levels of solubility in different types of solvent. Generally, lipophilic ("fat loving") drugs will demonstrate greater solubility in lipid and non-polar solvents than in water or other hydrophilic solvents, while the reverse will be true for hydrophilic ("water-loving") drugs. The generalisation is that "like dissolves like", although as for all generalisations this cannot be regarded as being a rule.

368. True solubility is reached at thermodynamic equilibrium. There can also be an apparent solubility level in which a drug's dissolution appears to have reached equilibrium but in fact has not. Apparent solubility can be higher or lower than equilibrium solubility.

Dissolution

369. Dissolution describes the process by which an API dissolves from a dosage form. The API must first come into contact with the solvent, dissolve into it and then move away from the remaining solid by diffusion. As drug molecules diffuse out of the diffusion layer which surrounds the dissolving API, further dissolution of molecules from the drug particle will occur. *In vivo*, dissolved drug molecules that have diffused away from the dissolving solid may then be removed from the GI fluids by the process of passive diffusion (or active transport) through the GI membrane moving into the plasma of the blood stream to be distributed around the body and to the site of action.

370. The factors that influence dissolution rate are clear from the Noyes-Whitney equation, first published in 1897:

$$dm/dt = kA\ (Cs - Ct)$$

where:

dm/dt = the dissolution rate

A = available surface area of the undissolved API for dissolution

Cs = solubility of the API (equilibrium solubility)

Ct = concentration of dissolved API in the bulk of the dissolution fluid at time t

k = a constant / term relating to diffusion of dissolved API away from the dissolving material and the thickness of the stagnant layer

371. The equation indicates that the rate of dissolution of a solid mass of drug may be enhanced by increasing the rate of diffusion away from the dissolving surface (by increasing the stirring speed for example), increasing its effective surface area or increasing the drug's solubility. When conducting dissolution testing *in vitro*, *in vivo* sink conditions (dissolution rate not hindered by the build-up of the Ct term in the Noyes Whitney equation) are mimicked by using a volume of dissolution medium that is at least five times the saturation volume.

Biopharmaceutics Classification System

372. The Biopharmaceutics Classification System (or "BCS") provides a system by which drug compounds may be categorised based on the biopharmaceutical properties fundamental to their absorption into the blood plasma i.e. solubility and intestinal permeability. It derives from a paper by Amidon *et al*. The BCS allocates drug compounds to one of four "classes" in accordance with these properties.

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

373. Drugs allocated to Class I are well-absorbed. As dissolution will occur very quickly, absorption rate may be controlled by the rate at which the stomach empties its contents into the small intestine which is the major site of absorption. Absorption for Class II drugs will typically be slower than that exhibited by Class I drugs. For Class II, drug dissolution will usually be the rate-limiting step for absorption. Class III drugs will have a slower rate of permeation than dissolution. As such, permeability will represent the rate-limiting step. Class IV drugs will have low rates of dissolution and permeation.

Dose number

374. The skilled formulator would be aware of a drug parameter called dose number as a matter of common general knowledge. The solubility referred to in the BCS classification table above is determined by the dose number. It is dimensionless and is defined as:

$$Do = (M_0 / V_0) / Cs$$

in which:

M_0 is the mass of drug administered (i.e. the dose);

V_0 is the volume of dissolution medium available in which the dose may dissolve (e.g. the volume of liquid in the stomach); and

Cs is the drug compound's aqueous solubility (determined experimentally).

375. Dose number is a way of characterising the solubility of a drug relative to the dose required in a systematic manner. Simply put, it may not matter if a drug has low aqueous solubility if the amount of drug actually required to be administered to the patient is itself low enough so that all the drug required dissolves. There were examples in the literature comparing two drugs which both had low aqueous solubility, but in which one drug had a much higher dose number than the other. The low dose number drug was easier to formulate than the high dose number drug. The example high dose number drug was called griseofulvin.

376. A different issue is whether the skilled team would take the trouble to determine what the dose number of a drug was at any particular stage of a development project. Prof Buckton gave convincing evidence that the skilled formulator would not determine the dose number at the outset. Prof Frijlink's evidence was effectively that it would be calculated. I preferred Prof Buckton on this but it is quite a narrow issue. I am sure the skilled formulator would have the general concept of the relationship between dose and drug's solubility well in mind. They would just not necessarily determine the dose number.

The 092 patent specification

377. The 092 patent is entitled "Beta-carboline drug products". The background of the invention section starts at para [0003] by noting that the biochemical, physiological and clinical effects of cGMP-specific PDE inhibitors suggest utility in a variety of disease states, noting that PDE5 is an attractive therapeutic target. After referring to Daugan, paragraphs [0005] and [0006] are as follows:

> "[0005] The poor solubility of many β-carboline compounds useful as PDE5 inhibitors prompted the development of coprecipitate preparations, as disclosed

> in PCT publication WO 96/38131 and Butler U.S. Patent No. 5,985,326. Briefly, coprecipitates of a β-carboline with polymeric hydroxypropylmethylcellulose phthalate, for example, were prepared, milled, mixed with excipients, and compressed into tablets for oral administration. Studies revealed, however, that difficulties arose in generating precisely reproducible lots of coprecipitate product, which makes use of coprecipitates less than ideal in pharmaceutical formulations.
>
> [0006] Additionally, clinical studies involving administration of coprecipitate tablets preliminarily revealed that maximum blood concentration of the β-carboline compound is achieved in 3 to 4 hours, with the average time for onset of therapeutic effect not yet precisely determined. In the treatment of sexual dysfunction, such as male erectile dysfunction or female sexual arousal disorder, however, a more rapid achievement of maximum blood concentration, along with a greater prospect for rapid onset of therapeutic effect, frequently is sought by individuals desiring more immediate and/or less prolonged effects. Accordingly, a need in the art continues to exist for orally administrable β-carboline compounds and β-carboline-containing pharmaceutical compositions having an ability to provide a therapeutic effect within a desirable, or at least acceptable, time frame."

378. This passage explains that the poor solubility of beta-carboline compounds useful as PDE5 inhibitors led to the development of co-precipitate formulations, but there were manufacturing problems with reproducibility. In addition, maximum blood concentration was only achieved in 3 to 4 hrs whereas for use in the treatment of sexual dysfunction, a more rapid achievement of maximum blood concentration was desired, in order to achieve a more rapid onset of therapeutic effect. The patent by Butler referred to in para [0005] is a patent from Glaxo relating to tadalafil.

379. In the summary of the invention section from para [0007] onwards, the 092 patent explains how it has been found that free drug forms of tadalafil having defined particle size characteristics provide compositions that exhibit rapid achievement of maximum blood concentration and a rapid onset of therapeutic PDE5 inhibitory effect (see paragraph [0009]). The relevant particle size characteristics are where at least 90% of the particles have a particle size of less than about 40 microns. In paragraph [0008] tadalafil is drawn as "formula (I)" and is named as "compound (I)" in the later paragraphs. The term "free drug" is defined later in the document (para [0024]) to refer to solid particles of tadalafil not intimately embedded in a polymeric coprecipitate.

380. The patent deals with the determination of the size of particles at paras [0037]-[0046]. In paras [0038]-[0044] it describes a method of determining the

particle size by use of laser diffraction. Paragraphs [0045]-[0046] describe determination of the particle size of free compound in a pharmaceutical composition by microscopy. The issues raised by these paragraphs are best addressed in the context of insufficiency.

381. Paragraph [0048] refers to dosing:

> "The specific dose of *[tadalafil]* administered according to this invention is, of course, determined by the particular circumstances surrounding the case including, for example, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose contains a nontoxic dosage level from about 1 to about 20 mg/day of *[tadalafil]*. Preferred daily doses generally are about 1 to about 20 mg/day, particularly 5 mg, 10 mg, and 20 mg tablets, administered as needed."

382. Paragraphs [0053]-[0059] refer to the free drug form of tadalafil formulated so as to produce a Cmax of 180 to 280 μg/L, and/or an AUC (0-24) of 2280 to 3560 μg·h/L, measured using a 10 mg dose of the compound. The patent goes on to explain that Cmax and AUC (0-24) in plasma is dose dependent, such that a 20mg dose ought to produce twice the Cmax and AUC of the 10mg dose, and a 5mg dose half those of the 10 mg dose.

383. There are then five examples:

(a) Example 1 is an *in vitro* dissolution test on various samples of tadalafil with differing particle size. 10mg of each sample was dissolved in 1L of aqueous 0.5% sodium lauryl sulfate (a surfactant) at 37°C.

(b) Example 2 shows the improvement in bioavailability provided by the invention over the co-precipitate formulation. With the co-precipitate, Tmax was not reached until 3.5 hrs. With the invention, it was reached in 2hrs.

(c) Example 3 is an *in vivo* study in which three tablets of tadalafil with different particle sizes are tested to determine their bioequivalence. These show that decreasing particle size increases Cmax, decreases Tmax and increases $AUC_{(0\text{-}24)}$ (save that decreasing particle size from 20μm to 8.4μm did not decrease Tmax).

(d) Examples 4 & 5 are formulation examples for 10 mg (example 4) and 5 mg and 20mg (both example 5) tablets.

384. The specification then turns to the claims.

Claim construction - 092

385. Claim 1 of 092 is a product claim relating to a composition of tadalafil. It also covers pharmaceutically acceptable salts and solvates of tadalafil but nothing turns on that. The claim is to a "free drug particulate form" of the drug. The claim then expressly requires the tadalafil to be solid particles not intimately

embedded in a polymeric co-precipitate. In fact, the definition of "free drug" in the document probably had that effect in any event. The final feature of the claim is that at least 90% of the particles have a particle size of less than about 40 microns. The debate whether this distribution is by number or by weight is best addressed in the context of insufficiency.

386. Product claims 2 to 4 limit the particle size to 25, 15 and 10μm respectively but as the case has developed nothing turns on these claims.

387. Product claims 8 and 9 relate to pharmaceutical compositions by reference to two pharmacokinetic parameters Cmax and $AUC_{(0-24)}$ defined by ranges. Nothing turns on the definitions as such. Claim 9 has a more narrowly defined AUC than claim 8. Lilly accepted that, on the obviousness case put against claim 1, claims 8 and 9 stand or fall with that claim. There is a point on novelty of these claims.

388. Claims 12 and 13 are use claims. They claim the use of the small particle size free drug particulate form of claims 1-4. The use claimed in claim 12 is "for use in a method of treatment", i.e. any method of treatment. It is not limited to a particular disease. Claim 13 is a Swiss style claim for the use of the product of claims 1-7 in treating sexual dysfunction. Male erectile dysfunction in particular is referred to in claim 14.

389. Claim 16 is a Swiss style claim to the use of a pharmaceutical composition according to claims 8 or 9 for treating sexual dysfunction. Claim 16 therefore has the pharmacokinetic parameters in claims to 8 and/or 9 incorporated within it.

390. Since claims 13 and 16 are limited by a particular use, achievement of that use is a functional technical feature of the claim. As such, in order to demonstrate that they are obvious, this has to be taken into account. Lilly also submitted the same goes for claim 12. I will assume, without deciding, that that is correct. In any event Lilly accepted that those three claims stand or fall together.

391. The feature which claim 19 adds to the claims from which it depends is the use of tadalafil for oral administration up to a maximum daily dose of 20mg. Neither side suggested that as a matter of construction this has a different meaning to the closely related wording in claim 1 of the 181 patent. I find it has the same meaning for the same reasons. The differences in the specifications do not lead to a different conclusion. Of course this claim is limited to up to 20 mg/day whereas claim 1 of 181 is up to 5 mg/day.

Priority -092

392. The question I have to decide on priority is whether the feature in claim 19 is entitled to priority. The key passage in the priority document is at p12 ln11-18 as follows:

> "The specific doses of a compound administered according to this invention will, of course, be

> determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level from about 1 to 20 mg/day of a particulate compound of the present invention. Preferred daily doses generally will be from about 1 to 10 mg/day, particularly of 5mg and 10mg tablets, administered once per day."

393. There are two issues, first whether this discloses the dosing feature of claim 19 and second whether it relates to tadalafil. As to the first issue, I refer back to the consideration of a very similar (but not identical) passage as part of the priority issue for 181 and the finding that a maximum daily dose is disclosed. The logic here is the same. In my judgment the passage in this priority document does disclose a daily dose of up to a maximum of 20 mg/day. The fact the words "about" and "typically" appear in the priority document does not make this a different invention from what is claimed on the construction of the claim I have arrived at. Neither side suggested that the fact the range in the priority document starts at 1mg mattered.

394. As to the second issue, the skilled reader would understand this passage as being applicable to tadalafil. It is correct that this passage is generic and it is also correct that the priority document, unlike the 092 patent, is widely drawn and relates to a class of beta-carboline compounds. However, the priority document clearly identifies tadalafil as a member of the class (as "Compound A"). The chemical name is given using the (6R-trans) terminology. The four examples in the priority document all relate to tadalafil. Tadalafil is clearly at the heart of the disclosure of the priority document. I find that claim 19, insofar as it is dependent on claims which are themselves entitled to priority, is entitled to priority.

Added matter - 092

395. The point is about claim 19 and is closely related to the priority issue. The relevant passage in the application as filed is at p17 ln23-27. It states;

> "A typical daily dose contains a nontoxic dosage level from about 1 to 20 mg/day of compound (I). Preferred daily doses generally are about 1 to about 20 mg/day, particularly 5 mg, 10 mg, and 20 mg tablets, administered as needed."

396. This passage is not identical to the one in the priority document but it is close enough that the points are the same. Save for what follows I would dismiss the added matter argument without anything further.

397. In cross-examination the following exchange took place with Dr Brock relating to the Anderson prior art to 181 (which is the application for 092):

17 Q. Now, on this, there is no mention in this document, Anderson,
18 of a maximum dose. That is right, is it not?
19 A. They talk of 1-20 mg and that the physician can ultimately
20 choose the dose.
21 Q. 1-20 are typical doses. There is no mention of a maximum
22 dose. Try and find the bit that I think you are referring to
23 is 17; is that right? The passage we looked at earlier.
24 A. Yes. I do not believe they cite a maximum dose.
(T6/825/17-24)

398. So the claimants submit that whilst Anderson contains teaching relating to what a "typical", "general" and "preferred" daily dose for tadalafil is in the passage above from p.17, there is no teaching relating to what a "maximum" daily dose is and claim 19 adds matter.

399. The trouble is that this all depends on what Dr Brock meant by "maximum" which takes one back to the arguments about claim construction which I resolved in relation to the 181 patent and which are applicable to 092. On the construction of claim 19 which I have identified, there is no added matter.

Novelty - 092

400. The argument is about novelty over Oren. It is novelty-only prior art under s2(3)/Art 54(3). Oren is concerned with tadalafil. It discloses dosing of 1mg to 10mg/day (p13 ln11-14). It has 13 examples of tadalafil formulations. There is no dispute that although it is only expressed for Examples 1 and 2, all of these formulations in fact have particle size distribution of d90 of 4 microns. Therefore these formulations would fall within claims 1 to 4 of the 092 patent but that does not matter because those claims are entitled to the 092 patent's claimed priority date and so Oren is not prior art against them. Oren is only prior art against any claim which is not entitled to priority. On my findings that means it is relevant prior art against claims 8, 9, 16 to 18 and 19 insofar as 19 is dependent on 16 to 18. Those claims are limited not by particle size but by pharmacokinetics. There is a clear teaching in Oren to administer the formulation in order to treat sexual dysfunction but there are no pharmacokinetic data in Oren to show what would happen if you did.

401. Lilly says that the only basis on which these claims could lack novelty is inevitable result and that this has not been proved. The claimants do not agree it has not been proved. One contention is that the patent shows that using a claimed particle size distribution gives the claimed pharmacokinetic parameters and that if that is not right, there must be insufficiency. While I sympathise with the rhetoric I am not convinced the logic is sound. The tests for inevitable result and sufficiency are not the same and the policy underlying them is not the same either. If a claim covers something which is the truly inevitable result of carrying out a prior teaching then that claim is monopolising something which was available to the skilled person without any knowledge contributed by the inventors. It makes sense that the public should not have to worry about such a patent. It lacks novelty. However when a skilled person is given the patent, they have a new teaching and a new goal in

view. Knowledge of that goal is likely to influence how they follow the teaching in the document. Even if they miss the target on the first shot, the patent has told them where to aim and, with straightforward trials and knowledge of the goal, they may reach the target. If so then the invention will still have been sufficiently disclosed even if the first shot at putting the invention into practice may be wide of the mark.

402. The law on inevitable result, with references to planting the flag, comes from ***General Tire*** [1972] RPC 457. This also discussed the idea that if something would infringe afterwards it must anticipate before. The concept was also discussed by Lord Hoffmann in ***Synthon*** at paragraph 23:

> "But the infringement must be not merely a possible or even likely consequence of performing the invention disclosed by the prior disclosure. It must be necessarily entailed. If there is more than one possible consequence, one cannot say that performing the disclosed invention will infringe. The flag has not been planted on the patented invention, although a person performing the invention disclosed by the prior art may carry it there by accident or (if he is aware of the patented invention) by design. Indeed, it may be obvious to do so. But the prior disclosure must be construed as it would have been understood by the skilled person at the date of the disclosure and not in the light of the subsequent patent."

403. Lilly referred to Laddie J in ***Inhale v Quadrant*** [2002] RPC 21. In that case the claim required a material with a glass transition temperature (Tg) of at least 20ºC. The judge found that the prior art referred to storage at room temperature and that it was extremely likely that the material therefore had a Tg of 20ºC. However for the prior art a Tg of 19.5ºC might have been enough and so there was no anticipation by disclosure. In the next paragraph (104) the judge said as follows:

> "104 I can therefore turn to the case on inevitable result. As I have said, in relation to this issue experiments were performed. This has produced a very large amount of evidence. Inhale has identified every single difference between the description of the process and apparatus in [*the prior art*] and that used in Quadrant's experiments and argues that the latter are neither a repetition of [*the prior art*] nor do they prove that a product within the claims of the patent would inevitably be made. Each of the points taken by Inhale has been addressed by Quadrant. However, it is not necessary to go through each of them because, for the reasons set out in the last preceding paragraph, it has not been proved that repetition of the teaching in the document would inevitably have produced something with a Tg *above 20°C* . Once again, it is overwhelmingly likely that such

> a Tg would have been achieved, but that is not enough for the purpose of anticipation."

404. I respectfully agree with Laddie J that even if it is overwhelmingly likely that an experiment would be set up in such a way that the result achieved would be within the claim, that is not enough for anticipation. That follows as a matter of principle. It is what the word "inevitable" is seeking to exclude. The result may be obvious but if, as here, one is concerned with novelty-only art that is of no significance.

405. However, it is important to distinguish between two different kinds of likelihood. Laddie J was not there talking about the standard of proof in civil cases and nor were the Houses of Lords in ***General Tire*** and in ***Synthon***. The standard of proof for the establishment of facts in patent cases is the balance of probabilities. In the EPO sometimes a different standard is or may be applied (e.g. "to the hilt") but to the extent that is what the EPO is doing, it is because the EPO is not the final word on validity and is not a national civil court. There is no warrant for applying a higher standard of proof to any of the facts in issue in a patent case. So one needs to be careful with what likelihood one is talking about. In ***Inhale*** the target was not precisely defined in the prior art and it was therefore not inevitable that a skilled person would arrive at the target in the claim (of which they were necessarily unaware). Without knowledge of the patent it was overwhelmingly likely that they would produce something with a Tg of at least 20ºC but it was not inevitable, because a Tg of 19.5ºC would have been sufficient for them. Hence no anticipation by inevitable result.

406. The point on standard of proof came up in the ***Nebivolol*** case ***Actavis v Janssen*** [2008] FSR 35. Here Floyd J had to decide if a product would have the relevant property. He held that it was overwhelmingly likely that it would and then said the following:

> "85. Is that finding good enough for an inevitable result? The legal requirement is that this feature of the claim be the inevitable result of carrying out the prior teaching. Does that mean that if there is some other possibility, even a fairly remote one, that some other result would follow, I should conclude the result is not inevitable? Or am I concerned to establish what, on the balance of probabilities would in fact occur? In my judgment, it is the latter approach which is correct. The inevitable result test does not require proof of individual facts to a quasi-criminal standard. It may be impossible to establish the relevant technical facts to that standard. It is another matter if the evidence establishes that sometimes one result will follow and sometimes another, depending on what conditions are used. But there is nothing of that kind suggested here. It is simply a question of what occurs in fact."

407. I respectfully agree. This is not in conflict with ***Inhale***, it is concerned with a different question.

408. In this case the target is clear. Oren teaches the skilled person to make a formulation with a d90 of 4 microns. That is the inevitable result of Oren. The question is whether a composition with that property necessarily has the claimed pharmacokinetics. This size range means the particles are smaller than the narrowest claimed range in the patent (claim 4 has a d90 of 10 microns). Mr Muirhead's evidence on this was not challenged. In paragraphs 59 to 66 Mr Muirhead analyses data available to him in the proceedings and expresses his opinion as follows:

> "I consider it highly likely that the formulation accordingly to Example 1 of Oren (which contains tadalafil with a d90 particle size of 4 μm) would exhibit Cmax and AUC values with the ranges […] stated by claims 8 and 9."

409. This is an opinion that it is highly likely that the product will have the claimed property. I accept that evidence and find that the product which would inevitably be produced by a skilled person following Oren would, as a matter of fact decided on the balance of probabilities, be within claims 8 and 9. Those claims therefore lack novelty and the same goes for all the claims dependent on them.

Obviousness – 092

410. The prior art relied on is Daugan. Although the priority dates and filing dates as between 181 and 092 differ there is no difference in substance. The analysis of what a skilled team would do given Daugan which was applicable for 181 is also applicable for 092. The focus this time is on formulation. Just to recap, it would be very obvious to start a clinical trials programme into orally administered tadalafil given Daugan and common general knowledge of sildenafil with a reasonable expectation that it would yield a safe, effective and tolerable treatment for erectile dysfunction.

411. As part of the pre-clinical studies the team would test the solubility of the drug. They would discover it was poorly soluble in water and in a low pH environment (such as in the stomach). They would also test permeability, at least initially by measuring the octanol/water partition coefficient and, I find, by then conducting a Caco-2 permeability assay. The conclusion would be that the drug had high permeability.

412. The formulator would be provided with information about likely dosing by other, clinically focussed, members of the team. At the stages at which the formulation would be developed (i.e. Phase I, IIa and at least before the results of the first dose ranging Phase IIb study) the dosing the team would be contemplating would be from 25mg to 100mg. On the footing that a decision to look into daily dosing had been taken, 10 mg would also be considered. The team would wish to ensure dose linearity, i.e. that the dose absorbed increased linearly with increasing dose delivered. The formulator would also

be told that a rapid onset of action, within 2 hours of administration, was required.

413. Putting this together, the formulator would therefore understand that the requirement is to administer a high dose relative to the solubility. The drug would be placed in BCS Class II. The formulation would be required to be able to work with doses ranging up to 100mg. With a low solubility, the drug would also have a low dissolution rate (because, as was common general knowledge, rate of dissolution is proportional to solubility). That matters because of the requirement for rapid onset.

414. Irrespective of the results of pre-clinical studies, Daugan itself also contains information which the formulator would note, from pages 12 to 16. First there are two formulations of direct compression tablets, then two wet granulation tablets and finally three capsules. The first two capsules are hard gelatin capsules. The third capsule presented is a soft gelatin capsule, said to comprise a suspension of active ingredient in Labrafil M1944CS (a surfactant). The dose of active ingredient in each is 50mg. In Daugan two active compounds are referred to, one of which is tadalafil, and the reader would understand these formulations to be as applicable to tadalafil as the other compound.

415. Prof Buckton's view was that these formulations indicate to the formulator that these compounds are poorly soluble. The presence of sodium lauryl sulfate in the second direct compression tablet formulation indicates that compounds A and B are hydrophobic. The first wet granulation formulation was a solid dispersion and the last soft capsule formulation would be seen as an attempt at a lipid solution, albeit as Prof Buckton noted it may not have been entirely successful as it is referred to as a suspension. I accept all this evidence.

416. Lilly's position is that the skilled person would see that the authors of Daugan had tried two well-known methods for improving the solubility of poorly soluble drugs and would therefore conclude that it was thought necessary to do so. I accept that to this extent. The skilled person would see that the authors of Daugan had tried two well-known methods for improving the solubility of poorly soluble drugs. The team would conclude that the authors of Daugan did that because those authors thought the formulations were worth using.

417. It was common ground between Prof Buckton and Prof Frijlink that the skilled team at this point would consider micronisation. A major issue is about the skilled person's expectations. There is also a point on surfactants.

The skilled person's expectations of micronisation

418. When considering expectations, a relevant factor will be nature and range of possible alternative techniques to look at. The main ones which present themselves in addition to micronisation are to use soft gelatin capsules, cyclodextrins, salt formation (but that would be ruled out early), crystal forms/polymorphs, and nano-milling. These all have inherent difficulties of their own. Nano-milling would be regarded as particularly problematic. There is nothing to suggest that finding a different polymorph is realistic.

419. However, micronisation is not just an item in a list of common general knowledge techniques to be tried to improve the situation when one has a BCS class II drug, it is at the top of the list to be considered. Prof Buckton's opinion was that micronisation was the simplest option while Prof Frijlink agreed micronisation would be the first thing the skilled person would think about albeit the professor's opinion was also that it would be immediately dismissed. The Amidon paper from which the BCS classification derives bears on this too. The paper contains a section dealing with media and methodology to use in dissolution testing and the issue of trying to reflect *in vivo* conditions. Rather than quote the entire section, this extract is enough:

> "If the drug is a case 2 drug (high permeability, low solubility) then absorption from solution is faster than dissolution and sink conditions are likely to prevail *in vivo*. As a general rule one should maintain sink conditions in the dissolution media if possible, such that the drug dissolves in less that 20-30% of the dissolution media.
>
> Other factors which need to be considered, especially for case 2 drugs, are particle aggregation and the effective particle size *in vivo*. Quite often the first approach to increasing the dissolution rate of drugs in this class is micronization. This however, also increases the surface energy and hence potential for particle aggregation. When predicting *in vivo* bioavailability from *in vitro* dissolution profiles, it is critical that the particle size used in the model reflect the *in vivo* particle size."
>
> (my emphasis)

420. A point on micronisation is that it can lead to aggregation. The formulator knows that. It would not deter them and would not diminish whatever expectation they had in achieving a good result. There was also an argument about ordered mixing. An ordered mix is one way of dealing with aggregation. Prof Buckton mentioned it in cross-examination but Lilly submitted ordered mixing was not established to be viable. I was not convinced this mattered either way. It was common ground that aggregation was a possible problem with micronisation, particularly so with hydrophobic drugs like tadalafil. But in my judgment the case does not turn on aggregation and therefore not on ordered mixing either.

421. One argument was that Daugan might put the skilled formulator off micronisation. Lilly's submission that Daugan's use of well-known methods for improving the solubility of poorly soluble drugs would have been seen as necessary was directed to this. The idea was that the reader would think Daugan must have either tried and failed with micronisation or dismissed micronisation on theoretical grounds. I do not accept this at all. It strikes me as highly speculative. Prof Buckton did not agree when it was put to him; his evidence was that Daugan's disclosure suggests the drug is poorly soluble and

he accepted that that may give the formulator difficulties. Prof Frijlink gave evidence of a related point but that was based on a different document, Butler.

422. A further issue is about what the purpose of micronisation actually is. The point is that as a matter of basic physics, making the particles smaller should increase the rate at which they dissolve but it does not alter the amount which will ultimately get into solution (i.e. the equilibrium solubility). So if the problem to be solved is to increase equilibrium solubility then micronisation cannot help. However one needs not to lose sight of the fact that micronisation is a well-known technique for increasing dissolution rate and given the need for rapid onset, as good a dissolution rate as possible would be desirable.

423. At this point it is convenient to deal with the argument about micronisation with a surfactant. The claimants' case, supported by Prof Buckton, was that a formulation which included micronised tadalafil as well as a surfactant was obvious. The surfactant took on extra significance as follows. In cross-examination Prof Buckton accepted, based on a passage from a textbook called Gibaldi, that for a high dose number drug such as griseofulvin and therefore for tadalafil, micronisation alone without solubilisation is unlikely to work. He accepted that, but maintained that that was why the skilled person would include a surfactant and that micronisation plus surfactant was obvious. It was put to him that he had not mentioned this in his first report and that this represented a shift in the professor's views. It was said to be an indication of a hindsight driven attempt to justify a conclusion he had reached at the outset in the absence of information about tadalafil, which, once he saw that tadalafil had such a high dose number, indicated the flaws in his approach. Sometimes this kind of point does indeed indicate that hindsight or *post hoc* justification has crept into an expert's analysis. The important considerations on this are as follows.

424. First, quite properly it was put to Prof Buckton in cross-examination. In answer to the point that he did not mention surfactants anywhere in the passage of his first report dealing with Daugan, he said: "I mention a conventional formulation. I cannot imagine this kind of formulation without a surfactant in it." In my judgment that represented the professor's genuine view which he had always held.

425. Second, as far as I am aware, although it was part of Lilly's case in opening that micronisation would not be expected to work because it would have no effect on solubility, until it was put to Prof Buckton in cross-examination emphasis had not been placed on the idea that the difference between success and failure with micronisation of tadalafil was the addition of a surfactant. The patent does not say that. The tablets in the examples include a surfactant but it is not commented upon. None of the claims mention the inclusion of a surfactant in the formulation. Claim 1 simply requires particles below 40 microns (d90).

426. Example 1 of the patent is a dissolution test of tadalafil and the reader would see that the concentration of the surfactant sodium lauryl sulfate in the dissolution medium was over the critical micelle concentration (CMC) and

that this has increased the compound's solubility in that experiment. This is a different issue. The fact high levels of surfactant are used in a dissolution test, which the evidence showed was normal for that sort of test, is a different point.

427. Third, in Prof Buckton's first report he expressed the view that micronisation was obvious. In his first report Prof Frijlink expressed the view that it was not. Prof Frijlink addressed two disadvantages of micronisation: aggregation and a reduction in wettability. Prof Frijlink explained that surfactants can be added to enhance wettability but cautioned about their possible toxicity and said that their use *in vivo* had to be tightly controlled. When Prof Buckton engaged with this part of Prof Frijlink's evidence in his reply report, the professor explained that surfactants were used very frequently in oral dosage forms and were known to increase absorption by wetting and by solubilisation through micelle formation. Later in his second report, when dealing with Daugan he said at paragraph 3.30 that:

> "In the case of tadalafil, which cannot form a salt in physiological conditions, the skilled formulator would first consider particle size reduction via micronisation, probably in conjunction with use of a surfactant.

428. The conclusion I reach from the written evidence is that the discussion about surfactants did not come into the case in a manner suggesting hindsight or backwards rationalisation on the part of Prof Buckton.

429. The point on micelle formation is as follows. To form micelles and thereby increase solubilisation the quantity of surfactant has to be above the concentration at which micelles are formed (the CMC). The quantity used in a formulation will not be high enough to reach that concentration in the bulk fluid but the professor's view was that at the surface of the dissolving particles the surfactant would be at a high local concentration sufficient to form micelles which would exist transiently and increase the apparent solubility of the drug.

430. Fourth, Prof Frijlink's evidence in cross-examination was that while he would not agree that including a surfactant when reducing particle size was standard, nor was it an unusual approach. In his opinion it was "something different", by which I understood him to mean rarer than standard but commoner than unusual. I accept that and if it differs from Prof Buckton's "very frequently", I prefer Prof Frijlink on that. Prof Frijlink agreed that the skilled person would at least consider including a surfactant, although he was not prepared to accept the skilled person would think it was likely to have an effect on increasing apparent solubility. He said if the amount of surfactant was low you may not form micelles or they may only form for a very short period and the effect on apparent solubility may be very, very small.

431. My conclusions on this surfactant issue are these. I reject the submission that Prof Buckton's evidence involved any sort of relevant shift or was hindsight driven. I find that the idea of using a surfactant together with micronisation was part of the common general knowledge. It would be an obvious thing to

do for a skilled formulator thinking of micronising tadalafil to include a surfactant in the formulation. They would do so in order to give micronisation the best chance it had to work. It would be regarded as helpful both as a wetting agent and as possibly aiding solubilisation. With the amount of surfactant which would be included, a micronised tadalafil formulation would work.

432. The major point made by Lilly, supported by Prof Frijlink, why the skilled formulator would not even try micronisation or at least would not think it would work, was concerned with thinking about what would happen in the gastrointestinal tract. Absorption into the systemic circulation generally has to take place in the small intestine. There can be absorption in the colon but it is not relevant. Prof Buckton did mention absorption in the colon in cross-examination more than was necessary. In that respect he was being argumentative but not in a manner which leads me to discount his evidence. It was very minor and Prof Frijlink occasionally had a similar tendency.

433. To be absorbed in the small intestine the drug has to be in solution. Liquid constantly leaves the stomach and passes into the small intestine. In the small intestine dissolved drug passes through the intestinal wall by various mechanisms, including passive diffusion driven by the concentration gradient across the wall and active transport. The mechanism which matters in this case is passive diffusion. If the concentration of drug in the small intestine is low, the driving force for the diffusion will be low (Fick's first law). Another factor affecting how the drug crosses the intestinal wall is permeability.

434. Readily soluble drugs will dissolve completely in the stomach, the dissolved drug will therefore pass into the small intestine. The concentration there will be relatively high and, subject to permeability, the drug will be absorbed.

435. There are three ways in which a poorly soluble drug may reach the small intestine. First, some but very little may dissolve in the stomach and pass into the small intestine for absorption. Second, the tablet will be designed to disintegrate e.g. by including a disintegrant. From this there may be very small drug particles available. They can pass out of the stomach in the same way as dissolved drug. They would then still need to dissolve in the small intestine. Third there is a periodic housekeeper wave which empties the stomach contents into the small intestine. The period between housekeeper waves can be up to 3 hours. Again once in the small intestine the drug would still need to dissolve to be absorbed.

436. Getting into the small intestine is only the first step. If the drug is poorly soluble then the driving force for absorption across the intestinal wall will be low. Material passes along the intestine over a period of 3 to 4 hours. In the context of this case one can assume that if the drug is not absorbed in the small intestine in that period, it will not be absorbed at all. The unabsorbed drug will be excreted. So even once the drug has reached the small intestine, the absorption may not be fast enough to get it all absorbed in time. The absorption may also be too slow to give sufficient systemic concentration for rapid onset of the therapeutic effect.

437. These considerations are part of the common general knowledge. They explain why high dose number drugs are known to be challenging. But one needs to take care not to overstate this. Neither side suggested that the skilled team would throw up its hands before testing anything.

438. One of the claimants' points was that the skilled formulator understood that the conditions which would be encountered in the context of tadalafil were "sink conditions". The point is that across the intestinal wall the circulation acts as a sink for any absorbed drug and since tadalafil is a BCS class II drug, the rate limiting step is not permeability across the intestinal wall but dissolution. I accept that, see for example the extract from Amidon quoted above. A different point is whether the skilled person would think that meant these sink conditions were the same as the sort of sink conditions one used *in vitro* for dissolution testing. They would not think that.

439. Prof Frijlink's opinion was that these considerations would lead the skilled person to think that micronisation would not be worth trying. The claimants characterised his opinion as being based on the idea that the stomach was a "closed system" but that is not an accurate characterisation of the professor's opinion.

440. Both experts were agreed that the mean gastric residence time of a disintegrating tablet in the stomach is about 90 minutes. One of the differences between them was as to the fraction of the drug that passes into the small intestine in the early part of that 90 minute period. Prof Buckton was of the view that approx. 50% would leave the stomach in the first 15 mins. Prof Frijlink's view was that leakage of fluid and undissolved particles of drug through the pylorus (the sphincter between the stomach and the intestine) is relatively slow and that a larger proportion of the drug particles and liquid (containing dissolved drug) is likely to remain in the stomach until the next housekeeper wave. He put the amount of drug leaving in the 90 mins as approx. 30%, but that if a housekeeper wave came in that period, it would be much more.

441. Lilly submitted that this difference was not particularly important because it was common ground that, unless tadalafil's solubility (or apparent solubility) can be increased, only a tiny fraction of a dose of tadalafil would dissolve in the stomach (about 1% of a 50mg dose in 250ml of medium). Therefore the vast majority of it will, if it is to be absorbed at all, have to dissolve in the small intestine in any event. Lilly argued that the issue of obviousness turns on whether the particles of tadalafil that arrive in the small intestine will be expected to dissolve rapidly enough and be absorbed rapidly enough to produce the required therapeutic effect to treat ED and achieve the required rapid onset of action.

442. I am not convinced that the issue is as unimportant as Lilly contends. Prof Buckton's view means that a significant amount of drug passes into the small intestine within 15 minutes. Prof Frijlink's approach is quite different, if in general only 30% has left the stomach after 90 minutes. From the point of view of a skilled formulator thinking about how tadalafil will behave and bearing in mind the requirement for rapid onset within 2 hours, the difference

between these two views is important. Prof Buckton gave a convincing explanation for his opinion, in that there is a constant leakage of dissolved drug and small disintegrated particles below 2mm from the stomach and an exponential rate of emptying. If the mean residence time for a drug is 1 ½ hrs, given the exponential rate the first 50% will be out in roughly 15 minutes because total expulsion takes about six half-lives. By contrast while Prof Frijlink did maintain his opinion in cross-examination, he did not support it with reasons, or at least with any reasons which engaged with those given by Prof Buckton. I prefer Prof Buckton's evidence on this issue.

443. The significance of this is that 50% of the drug (dissolved and small particles) will have reached the small intestine within 15 minutes of taking the tablet. Once in the small intestine the drug at least has a chance of being absorbed. As dissolved drug is absorbed, more drug will in turn go into solution to replace it. So increasing the rate of dissolution is important but nevertheless, as Lilly contends, with a low solubility drug the driving force behind absorption itself will still be low because the drug has low solubility and drug still has to diffuse in the intestine to the wall to be absorbed.

444. Another way of thinking about the problem is that unless solubility could be increased, which particle size reduction alone cannot do, the limited residence time in the gastrointestinal tract could place a limit on the amount of drug which could be absorbed regardless of the size of the dose in the tablet, preventing dose linearity. Lilly relied on a paper by two authors at Pfizer in 1996 (Swindell and Pearson) to illustrate the concern and suggested that unless solubility of tadalafil was improved, the limit would be 9mg. I accept the general concept rather than the number. Swindell and Pearson itself was not common general knowledge.

445. In the end however there is a danger of over-thinking all this. The concept of a dose number is a way of making concrete the idea which a skilled formulator would understand anyway that trying to deliver a high dose of a low solubility drug is harder than trying to deliver a low dose of the same low solubility drug. The reasons the expedients exist for trying to deal with low solubility drugs are because of all these considerations.

446. Another example of over-thinking was an argument that something significant depended on the skilled formulator thinking that a non-micronised formulation would achieve supersaturation. I think this was tied up with what were said to be the reasons why the skilled person would assume micronisation of tadalafil had failed or been dismissed without testing and so, if the only formulations which were thought to work in the prior art were ones which achieved supersaturation, micronisation alone, which can't, must not be viable. The skilled formulator would not think like this.

447. One way of examining the difference between Prof Frijlink and Prof Buckton was based on their evidence about how the formulator would approach their task in general. Prof Buckton's view was that the skilled person would always try to apply the "KISS" approach ("Keep It Simple Stupid"). Prof Frijlink agreed that the formulator would always consider simple methods before complex ones. When asked if it was an empirical art, Prof Frijlink said

there was a lot of theory in formulation development but accepted there was a lot of testing too.

448. Effectively Prof Frijlink's core reason for not using micronisation is that it would be dismissed on theoretical grounds, based on considering the extremely high dose number and what might happen in the gastrointestinal tract, without testing. Prof Buckton's approach was different. He did not agree that the skilled person would determine the dose number at initial stages because, as he put it "it is not going to change my view of life". His point was that the skilled person knows that the higher the dose and the lower the solubility, the harder it will be to achieve full bioavailability. He explained that the higher the dose is, the formulator's task gets harder for all the formulation strategies which have been suggested. So his view was that it does not alter the way things go. I preferred Prof Buckton's evidence about how the skilled formulator would approach their task to that of Prof Frijlink. I accept of course that formulation science has a firm theoretical basis in physics, chemistry and biology but I do not believe the skilled formulator would not test micronisation at all on theoretical grounds. They would test it. Accordingly Prof Frijlink's reasons, if I place weight on them, would tend to negate any expectation of success even if they do not go far enough to stop the test.

449. Prof Buckton's view on prospects of success was summed up in this passage:

> T7/1076/6-22:
> 6 Q. Let me understand I am clear on your evidence. Your evidence
> 7 is that you would go for the micronised formula first, not
> 8 because you think it is likely to work, but because it is the
> 9 most simple one?
> 10 A. I think it is likely to work. I did not say it was not likely
> 11 to work. I said all of these are likely to work. But it has
> 12 a huge advantage in as being the most routine,
> 13 straightforward, robust formulation. There is an enormous
> 14 advantage for it.
> 15 Q. I need to pick you up on that one. You say you expect it to
> 16 work. You have spent most of this morning telling his
> 17 Lordship that you cannot predict whether they will work.
> 18 A. Maybe we should be clear on the definition of work. I expect
> 19 it to improve things. As I just said to you, I cannot tell
> 20 you in a clinical trial whether any of these formulations are
> 21 going to achieve, you know, the particular goal of the
> 22 clinical trial. That is, you know, a biological outcome. But
> 23 I have an expectation that all of these will be better than
> 24 not doing anything.

450. In other words, the professor's view was that the skilled team would test a micronised formulation of tadalafil (including a surfactant). They would expect it to improve things, given the poor solubility of tadalafil and relatively high dose required. They could not tell whether any of the various formulations including the micronised one and the others advanced by Lilly would achieve the desired goal in a clinical trial. But their expectation is that all of them would be better than not doing anything.

451. If I consider Prof Frijlink's views as reasons to reduce the expectation of success, I do not believe they represent the thinking of the skilled team because while these are not the only foundations for his view, key foundations are an approach to timing in the GI tract which is not one the skilled team would adopt and the idea that the skilled person would be put off micronisation by Daugan, which I do not accept either.

452. I find that Prof Buckton's approach explained in cross-examination above represents the thinking of the skilled team. They would test micronised tadalafil (with surfactant). It is the simplest approach, the first on the list, and it would not be dismissed on theoretical grounds. They would have a clear expectation that it would improve things. They would test some of the other approaches but would not expect any of those others to work any better.

453. The question is whether that is sufficient to make the invention obvious. If the relevant standard is as high as Jacob LJ put it in ***St Gobain*** [2005] EWCA Civ 177 at paragraph 35 ("more or less self-evident that what is being tested ought to work") then I should reject the obviousness case. However as Floyd J said in ***Omnipharm*** [2011] EWHC 3393 (Pat) that formulation of the test was explained by Lord Hoffmann in ***Conor v Angiotech*** [2007] EWCA Civ 5 as a "fair expectation of success" with the degree of expectation depending on the facts of the case. Moreover in ***Teva v Leo*** when Jacob LJ referred again to paragraph 35 of ***St Gobain***, the passage quoted did not include the sentence about "more or less self-evident". On the facts of this case I do not believe the ***St Gobain*** way of putting the question is the appropriate one.

454. What I have well in mind is the passage in paragraph 35 of ***St Gobain*** which was cited in ***Teva v Leo***, that :

> "Mere possible inclusion of something within a research programme on the basis you will find out more and something might turn up is not enough. If it were otherwise there would be few inventions which were patentable. The only research which would be worthwhile (because of the prospect of protection) would be in areas totally devoid of prospect."

455. In no sense can it be said that the micronised formulation was being included only on the basis that the skilled formulator will "find out more" or that "something might turn up". Formulation in general and the testing of putative formulations in particular is an inevitable and necessary part of what is a very obvious clinical programme in the light of Daugan. Micronisation in these circumstances will be top of the skilled formulator's list and including a surfactant would not be inventive.

456. Lilly also submitted that the Butler patent application WO 96/38131 filed by Glaxo on tadalafil represented secondary evidence of non-obviousness. Butler is directed to methods of producing a solid dispersion of a poorly soluble drug. One of the two drugs is tadalafil. I do not place much weight on this. It is the same argument as the submission that the reader of Daugan would think the authors thought it was necessary to do this. I disagree for the same reasons as

before. Butler indicates that Glaxo thought what is disclosed was worthwhile but it does not indicate they thought it was necessary to do this because micronisation was not worth doing.

457. In my judgment micronised tadalafil in a formulation for the treatment of erectile dysfunction is obvious over Daugan. Considering the same factors identified before in relation to 181:

i) In terms of motives to find a solution to the problem the patent addresses, the skilled team would be highly motived by Daugan and the success of sildenafil to investigate tadalafil as a treatment for erectile dysfunction.

ii) As for possible avenues of research, overall tadalafil would be obvious to investigate. With low solubility and given the high dose required relative to it (i.e. a high dose number) there are some but not many options to consider. Top of the list is micronisation. It is simple and well known. The micronised formulation would include a surfactant.

iii) In terms of effort, overall the programme would involve very substantial resources of time, money and people but it would be pursued. The impetus to look at possible formulations would be substantial. At the point the formulations were being tested, the team would not have an alternative successful avenue available to them.

iv) Overall the team would embark on the project with a reasonable expectation of success in establishing tadalafil as a safe, tolerable and effective treatment for erectile dysfunction. The team would not know for sure that tadalafil could be formulated successfully but they would not give up without testing a fairly short list of expedients, of which micronisation would be one. In relation to the test of the formulation itself the team would have a high expectation that micronisation would improve the formulation. I have rejected Prof Frijlink's views on the skilled team's expectations of success both based on timings in the gastrointestinal tract and based on inferences from Daugan.

v) In terms of unexpected or surprising results, the low solubility of tadalafil is not unexpected although it does present a problem for the team. Nevertheless it is a problem the team is familiar with in general terms. The team would not be surprised that micronisation worked.

vi) The only significant value judgment which would be required of a skilled team in a programme which reached the claimed invention would be to test a micronised formulation of tadalafil (including a surfactant). That would not be a difficult decision.

458. I find that claim 1 of 092 is obvious. The same goes for the use claims. The point of the project would be to produce an effective treatment for erectile dysfunction and the expectations I have referred to are in that context.

Insufficiency - 092

459. The claimants take these points:

i) Claims which are limited only by pharmacokinetic properties and not by particle size are insufficient as being too broad. This applies to claims 8, 9 and 16 to 19 (subject to dependency);

ii) Claim 12 is insufficient as it is ambiguous or too broad because it is not limited to sexual dysfunction and covers any disease;and

iii) Claims 1 to 7 are insufficient because the way they claim a particle size distribution is truly ambiguous.

Claims limited by pharmacokinetic properties

460. One way to put an invention into practice is sometimes enough but not always. Ultimately the law is that a claim must be commensurate with the technical contribution made by the patent. If it is not, then the claim is invalid for insufficiency (see ***Biogen v Medeva*** [1997] RPC 1 and ***Generics v Lundbeck*** [2009] RPC 13).

461. Although not obvious at first sight, when one examines the set of claims of the 092 patent, it consists of two distinct sub-sets (with one exception). One subset is claims 1 to 7 and 12 to 15. They are all limited by particle size. They are all limited to micronised tadalafil. The other subset is claims 8, 9 and 16 to 18. All the claims in this subset are limited by pharmacokinetic properties. They are not limited by particle size at all. They are not restricted to micronised tadalafil. The one exception is claim 19. It is dependent on claims in either subset. However, it is really two claims, one version dependent on the micronised tadalafil claims and the other based on the pharmacokinetic properties claims. There is no claim in the 092 patent which claims a micronised form of tadalafil which has the defined pharmacokinetic properties.

462. For the purpose of this issue I will assume that the claimed invention is not obvious.

463. Lilly's case is that a skilled team given the patent would make micronised tadalafil and with the patent's disclosure would be able to make a product which had the relevant pharmacokinetics. Although at one stage that appeared to be in issue, it is manifest on the evidence of both Prof Frijlink (in his report) and Prof Buckton (in cross-examination) that a skilled team given the patent would be able to make the required micronised tadalafil products and that they would be able to ensure they had the required pharmacokinetics. Even if the first go at a micronised product did not fulfil the pharmacokinetic properties, the team would have no undue difficulty adjusting the formulation appropriately to achieve the desired result (e.g. by adjusting the particle size distribution).

464. The claimants' point is that the subset of claims limited by pharmacokinetic properties claims more than micronised tadalafil formulations. The fact that the patent enables one way of reaching the claimed result – micronisation –

does not justify a claim to all ways to the end result. There was an argument about whether the claims covered a solid dispersion of tadalafil. Part of it seemed to involve an unpleaded classic insufficiency argument but I am not prepared to entertain that; the point in issue is breadth of claim. Lilly pointed out that claim 8, from which all the relevant claims depend, refers to a free drug form of tadalafil. By the definition given in the patent, the free drug form must be in the form of solid particles and excludes a solid dispersion. It also excludes soft gelatin capsules, and cyclodextrin complexes are excluded because in those forms the drug is not in particule form. I accept that submission.

465. However, the pharmacokinetic properties are defined by reference to the composition as a whole. What if, as a matter of interpretation, as long as the composition contains free drug form of tadalafil (clause (a)) and an excipient (clause (b)), the composition could also contain other forms of tadalafil such as a solid dispersion, soft gelatine capsule, or cyclodextrin form etc.? In my judgment if that is the true construction of the claim then it would make ***Biogen*** insufficient. Stated at its broadest, the technical contribution of the patent is that tadalafil which has been processed, by micronisation, so as to produce the sorts of particle size distribution described and claimed in the patent and claimed, has pharmacokinetic properties which make it an effective treatment for sexual dysfunction. The technical contribution is not the pharmacokinetic properties divorced from the means by which they are achieved. That is not how the skilled reader would understand the document and it is not consistent with the state of the art even assuming claim 1 involves an inventive step. A rapid onset treatment for sexual dysfunction was obviously desirable to the skilled team by the priority date (see the obviousness section above). Moreover the document acknowledges in the background section that rapid onset of the therapeutic effect is frequently sought by patients (paragraph [0006]).

466. Although one might be tempted to read the claim more narrowly so that the reference to a "free drug form" of tadalafil is taken to describe the form of all the tadalafil in the composition, paragraphs [0052] and [0057] of the patent are against that construction. They expressly contemplate, as an embodiment of the invention, a composition which is a mixture of the free drug form of tadalafil admixed with the coprecipitate form of tadalafil. The composition could be a solid or a suspension. Paragraph [0052] refers to bimodal delivery and is presumably contemplating the idea that the free drug form is micronised and therefore responsible for rapid onset whereas the coprecipitate gives the slower delivery. Claiming that sort of thing would be commensurate with the technical contribution but the claim is not so limited. Paragraph [0057] includes the idea that a mixed composition has the Cmax and $AUC_{(0\text{-}24)}$ values with the claimed range (there may be a transposition of digits – 3650/3560 but nothing turns on that) and there is no basis in the evidence to say this does not work (that would be part of the unpleaded insufficiency objection I have not allowed). This makes sense on the footing that a composition which is largely in the form of the micronised material could achieve that result. However the claim is not so limited and does not require micronised material at all. In other words the claim covers compositions which consist of a mixture of any

amount of free drug form of tadalafil (which may or may not be micronised) together with other forms of tadalafil such as cyclodextrin complexes or that used in soft gelatin capsules. Therefore the claim has the wide scope identified above which is not commensurate with the technical contribution.

467. I find that claim 8 is insufficient and necessarily therefore so are claims 9, 16 to 18 and, insofar as dependent on them, claim 19.

Claim 12

468. The points raised against claim 12 were not pleaded however Lilly did not object because, it submitted, the points were bad. I agree. Claim 12 is not ambiguous, it is broad. It is not limited to a particular disease. This is a form of claim, not limited to a particular disease, which the EPO permits both for new compounds (which this isn't) or new compositions (which this is). The logic is based on EPC Art 54(4), see e.g. the Guidelines for Examination (Nov 2015) G-II paragraph 4.2. It is not insufficient on these grounds.

Claims 1 to 7 - particle size distribution

469. There is no doubt that claim ambiguity can lead to insufficiency. I tried to review the law on this topic earlier this year taking into account all the relevant material, the terms of the EPC, uninfringeable claims and so on, in ***Unwired Planet v Huawei and Samsung - Trial C - Inter RAT transfer*** [2016] EWHC 576 (Pat) at paragraphs 148 to 163. Rather than repeat it all, I will restate my conclusions on the legal principles by repeating the last two paragraphs of the analysis:

470. In ***Generics v Yeda*** [2012] EWHC 1848 (Pat) Arnold J said as follows:

> "… it is necessary to distinguish between claims that are difficult to construe or that have a "fuzzy boundary" (in the words of Lord Hoffmann in ***Kirin-Amgen Inc v Hoechst Marion Roussel Ltd*** [2004] UKHL 46, [2005] RPC 9 at [126]) on the one hand from claims that are truly ambiguous on the other. It is regrettably common for claims to be difficult to construe, but the court will nevertheless strive to give such claims a sensible meaning having regard to the inventor's purpose. It is also common for claims to have a fuzzy boundary, because an integer of the claim involves some question of degree or an imprecise functional limitation. It is well established that is not itself objectionable. If a claim is truly ambiguous, so that it is unclear what is the correct test to determine whether or not a product or process infringes, however, then the claim is insufficient, …."
>
> [In this case ambiguity was rejected on the facts.]

471. Pulling [*all the analysis in* ***Unwired Planet***] together, I agree that claims can often be difficult to construe. Sometimes those difficulties are due to avoidable

obscurity for which the patentee should get no sympathy, but it can be because trying fairly to describe an invention in words is not always an easy task. I also agree with Arnold J that the existence of a fuzzy boundary in a claim is not objectionable. The contrast is between that and a claim which is truly ambiguous. The factual circumstances in which such a truly ambiguous claim has been identified so far in the modern law (***Kirin-Amgen*** and ***Sandvik v Kennametal*** [2011] EWHC 3311 (Pat)) are ones which depend on carrying out a technical test to find out if a product or process is within the claim or not. If the skilled person cannot know whether they are carrying out the right test, then the claim is truly ambiguous and therefore insufficient. That makes sense. However, while the principle cannot be limited just to technical tests, after all ***SmithKline Beecham v Apotex*** [2004] EWCA Civ 1568 was not that sort of case, nevertheless it does not apply simply because one can imagine difficult cases to judge at the edge of a claim. When a defendant has been found to infringe, demonstrating that the claim's scope is at least clear enough to work that out, an argument that the claim should be regarded as truly ambiguous is likely to be met with scepticism.

472. Claim 1 requires a particle size distribution in which at least 90% of the particles have a particle size of less than about 40 microns. The claimants' case is that the skilled person would understand he could use either a volume distribution or a number distribution or both. But these two distributions produce radically different answers and so the claim is truly ambiguous. The test to be applied to decide if one is inside or outside the claim has a fatal ambiguity in it.

473. If the claim has that construction then I am sure it would be insufficient. Lilly did not suggest otherwise and I find that it would be. Lilly's answer is that the claim would not be understood that way. On the contrary the claim is to a volume distribution (or a weight distribution, which is for this purpose the same thing). On that basis there is no problem for the skilled person and no ambiguity. So the issue turns entirely on a point on construction.

474. The words in claim 1 read in isolation are apt to cover either or both kinds of distribution. The claim is referring to the distribution as it exists in the final composition but that does not mean it has to be measured that way. The easiest stage to measure particle size is at the raw material stage i.e. on the API. Once the API particles have been made, the tabletting process will make things stick together but it will not make the particles themselves any bigger. If anything the bigger ones will break up into smaller particles. The point is that the answer to the rival construction arguments is not to be found from the words of the claim in isolation.

475. The point is really quite simple. If I have six cans of fizzy drink and one 2 litre bottle then, taking a can as 1/3 litre, I can describe what I have in terms of a size distribution in two ways. Suppose I have lunch boxes which can only accommodate ½ litre sized container. To consider a number distribution one counts the containers (or particles). Expressed by number, 86% of the containers (6/7) have a size less than ½ litre. On the other hand, to consider a volume distribution one counts or measures the total volume or mass of material contained in the containers (or particles). Expressed by volume, half

the drink is in containers less than ½ litre in size. So in the volume distribution, the containers less than ½ litre in size represent 50% of the drink. Thus depending on whether the distribution is to be expressed by number or by volume the same distribution could be expressed as 50% or 86%. This is all common ground and explains why, if the claim is construed to cover both, it is truly ambiguous. Lilly did not suggest that the fact that one could imagine cases in which both distributions put you on the same side of the line was enough to avoid the objection. On the facts of this case I think that is right. The fact that there could be some extreme distributions for which the problem does not arise cannot help. This is not a case of a puzzle set at the edge of a claim (c.f. ***General Tire***).

476. The relevant common general knowledge of the skilled reader, who would be a formulator for this purpose, was not in dispute. They would understand particle size distributions, how to measure them and how to express those measurements. They would know that the most popular way to measure particle size was by laser scattering and that these systems reported a volume distribution. They would know that a laser scattering system could also be programmed to report a number distribution if that was required but would be well aware that they were normally set to report volume distribution. They would also know that microscopy could be used and that these methods produce a number distribution. Just as laser scattering generally reports by volume but can be set to report by number, so a number distribution can be expressed as by volume distribution based on certain assumptions (see below).

477. In cross-examination Prof Frijlink's evidence was that the formulator would like to see volume distribution, and not the number distribution. Prof Buckton agreed that in the pharmaceutical industry, by volume was the preferred distribution, whereas other industries find the number distribution enormously useful. The reason for this is not hard to fathom. What matters in the pharmaceutical industry is the amount of drug not the number of particles. If (as here) the small particles are the ones which will dissolve quickly enough to be useful, what one wants to know is how much of the drug is in that form.

478. I find that the skilled formulator's common general knowledge was that a volume distribution would be what a formulator would wish to use.

479. A standard way to report particle size distribution is by using d-values in which, for example: d10 means the diameter of particles below which 10% of the particles fall and d50 refers to 50%, etc. This is based on an assumption that the particles are spheres. In the real world they may not be spherical at all and that can complicate matters but the skilled formulator is aware of this. The difference between volume and number distribution can also be understood when one considers collections of spherical particles. As the radius of a spherical particle increases, its volume (and therefore the mass of drug it represents) rises with the cube of the radius. So a single 10 micron diameter particle contains 1000 times more drug than a single 1 micron diameter particle. Say one had one each of these particles. By number 50% of the particles have a diameter less than 10 microns but by volume only 0.1% of the drug is in particles of less than 10 microns. That is why it matters how to characterise the distribution. The skilled formulator knows this.

480. If the particles are all truly spherical then one can readily convert between number and volume distributions but in practice they are not and there are significant errors associated with real conversions, as Prof Buckton explained in cross-examination.

481. Turning to the patent, the claimants' case was that the disclosure expressly contemplates using either number or volume. Lilly tried hard to argue to the contrary. To the extent that it is a matter directly for the evidence of the experts rather than a matter in which the experts educate the court so that the court can then construe the specification, I did not find Prof Frijlink's evidence on this particular topic to be convincing.

482. The passage in the patent concerned with measuring particle size starts at paragraph [0037]. It makes clear that the examples are non-limiting. There is a cross-reference to a US Patent 4,605,517 from Sterling Drug Inc.. That patent is talking about a number distribution determined by microscopy (col 4 ln57-61). Prof Frijlink pointed out it also refers to measuring surface area but that is irrelevant.

483. Next in paragraphs [0038] and [0039] laser scattering is discussed. The skilled reader would understand the distribution produced would generally be a volume distribution. The samples tested here are the API before being put into a tablet. The words "spherical volume diameter" appear here and elsewhere. That has nothing to do with whether the size distribution is expressed by volume or by number. It is concerned with the standard way of ascribing a notional diameter to irregularly shaped particles by treating them as a sphere of equivalent volume and taking the diameter of that notional sphere.

484. Then at paragraph [0040] there is a discussion which the claimants submitted shows the patent contemplating expressing the distribution either by number or by volume. Lilly contends that the key sentence is not particularly clear. I disagree. The words refer to plotting "cumulative frequency vs diameter, or in other methods weight vs diameter, usually adopting percentage undersize values for the cumulative frequency or weight". In my judgment this plainly describes plotting two different distributions by percentage undersize value. One of them is cumulative frequency, i.e. number of particles, and the other is weight (which is equivalent to volume). There is nothing odd about this since the skilled person knows that a laser scattering machine can be told to report either way.

485. Paragraphs [0041] to [0043] again refer to laser scattering. Again, the skilled reader would understand the distribution produced would generally be a volume distribution.

486. Paragraph [0044] explains that the raw drug can then be made into tablets and paragraphs [0045] and [0046] describe using a microscope to examine the particle size distribution. The point is that one cannot sensibly do laser scattering because even after the dissolving step to remove some excipients, the sample will have other material present too. The patent explains that the crystalline tadalafil can be visually differentiated from amorphous

composition ingredients. The particle size is determined by visual inspection and comparison with standardised particles of known size. Lilly submitted this meant or included the possibility of using a standardised sample with a given size distribution and comparing that, as a distribution, to a test sample. Prof Buckton did not agree and Prof Frijlink's evidence to support this was particularly unconvincing. I reject that construction. Paragraphs [0045] and [0046] would be understood to describe a visual inspection technique using standardised particles of known size (not size distribution) so as to calibrate the technique. Particles would be counted. The result would be expressed by number.

487. So the specification would be understood to contemplate expressing particle size distributions both by number and by volume. The claimants contend that this means the claim is truly ambiguous and insufficient. I do not agree. The claimants' submission overlooks the common general knowledge of the skilled formulator. The skilled formulator prefers volume, knows that the two approaches are possible but also knows that they give radically different results. So if the claim expressly called for a volume distribution the reader would not be surprised. It is their preferred approach. Equally a claim which expressly called for a number distribution would be readily understood. However, the one thing the skilled reader would think would be decidedly odd would be the idea that the inventors intended that the boundary of the claim could be determined by either or both approaches. That makes no sense. It would be readily apparent to the skilled reader that such a construction made the claim hopelessly ambiguous. They would think the inventors must have meant one or the other, no rational formulator would cover both. One can always be converted into the other albeit this can introduce significant error.

488. Of course it would have been a simple matter to clear this up by stating expressly which distribution was being referred to and one possibility is that the draughtsman was deliberately being vague and trying to hedge their bets by allowing for either. I do not think that is what has happened nor do I think the reader would think that is what has happened.

489. The skilled reader would reject, at least provisionally, the idea that the claim covers both or either, and ask which of the two kinds of distribution is the one the inventors must have meant. Only if they could not answer that question would the claim be ambiguous. However, the conclusion is simple. A volume distribution is the one preferred in the pharmaceutical industry and for good reason. Given that ultimately what one wants to deliver to the patient is tadalafil molecules rather than particles as such, it makes sense to think of the distribution that way. That is consistent with the use of laser scattering to produce a volume distribution for the API. The skilled reader would see that the only reason a number distribution is determined at the end with microscopy is because there is no alternative. It could always be converted albeit with errors. Reading the document as a whole and in the light of the common general knowledge the skilled reader might well start with a doubt about it but they would arrive at one answer. The claim requires a volume distribution. I reject this ground of insufficiency.

Infringement - 092

490. The only distinct infringement issue relates to claim 19 and the SmPC. Since the claimed limit is 20 mg/day, it would be infringed if it was valid. The question of *quia timet* infringement actions relates as much to 092 as to 181 and the answer is the same.

Conclusion

491. I find that:

i) At least claim 7 of the 181 patent is valid and infringed;

ii) All the claims of the 092 patent are invalid.

Annex 1 – relevant claims of the 181 patent

In addition to claim 1, the relevant claims of the 181 patent are:

2. The dosage form of claim 1 comprising 2.5mg of the compound in unit dosage form.

3. The dosage form of claim 1 comprising 5mg of the compound in unit dosage form.

6. The dosage form of any of claims 1 through 3 for use in treating a condition where inhibition of PDE5 is desirable.

7. The dosage form of claim 6 wherein the condition is a sexual dysfunction.

10. Use of a unit dose containing 1 to 5 mg of a compound having the structure [*of tadalafil*] for the manufacture of a medicament for administration up to a maximum total dose of 5 mg of said compound per day in a method of treating sexual dysfunction in a patient in need thereof.

12. The use of Claim 10 or 11, wherein the unit dose contains 2.5 mg of the compound.

13. The use of Claim 10 or 11, wherein the unit dose contains 5 mg of the compound.

Annex 2 – relevant claims of the 092 patent

2. The free drug particulate form of claim 1 wherein at least 90% of the particles have a particle size of less than about 25 microns.

3. The free drug particulate form of claim 1 wherein at least 90% of the particles have a particle size of less than about 15 microns.

4. The free drug particulate form of claim 1 wherein at least 90% of the particles have a particle size of less than about 10 microns.

8. A pharmaceutical composition comprising:

(a) a free drug form of a compound having the formula of [*tadalafil*] and pharmaceutically-acceptable salts and solvates thereof, in which the compound is present as solid particles not intimately embedded in a polymeric co-precipitate; and

(b) one or more pharmaceutically-acceptable carriers, diluents, or, excipients.

wherein the composition exhibits a Cmax of 180 to 280 micrograms/litre or an AUC (0-24) of 2280 to 3560 microgram hour/litre, measured using a 10 milligram dose of the compound.

9. The composition of claim 8 wherein the composition exhibits a Cmax of about 180 to about 280 micrograms/litre and an AUC (0-24) of 2280 to 3560 microgram.hour/litre.

12. A free drug particulate form according to any one of claims 1 to 4 for use in a method of treatment.

13. Use of particles of a free drug particulate form according to any one of claims 1 to 4 or a pharmaceutical composition according to any one of claims 5 to 7 for the manufacture of a medicament for the treatment of sexual dysfunction.

14. The use of claim 13 wherein the sexual dysfunction is male erectile dysfunction.

15. The use of claim 13 wherein the sexual dysfunction is female sexual arousal disorder.

16. Use of a pharmaceutical composition according to claim 8 or 9 for the manufacture of a medicament for the treatment sexual dysfunction.

17. The use of claim 16 wherein the sexual dysfunction is male erectile dysfunction,

18. The use of claim 16 wherein the sexual dysfunction is female sexual arousal disorder.

19. The use of anyone of claims 13 to 18, wherein the medicament is formulated for oral administration up to a maximum daily dose of 20 mg per day.