Intellectual Property Office

BL O/136/22

16 February 2022

COUNCIL REGULATION (EC) 469/2009
CONCERNING THE CREATION OF A
SUPPLEMENTARY PROTECTION CERTIFICATE
FOR MEDICINAL PRODUCTS

APPLICANT	Ethicon, Inc., and Omrix Biopharmaceuticals, Inc
ISSUE	Whether application for supplementary protection certificate SPC/GB14/029 meets the requirements of Article 3(d) of the Regulation
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 This decision relates to the application for supplementary protection certificate ("SPC") SPC/GB14/029 ("the application") for a combination of three active ingredients, i.e., thrombin, fibrinogen and oxidised regenerated cellulose, filed in the names of Ethicon, Inc., and Omrix Biopharmaceuticals, Inc. ("the applicants")[1].

2 The SPC application was filed on 24 March 2014, and relies on basic patent EP(UK) 1809343 B1, entitled "*A reinforced absorbable multi-layered hemostatic wound dressing and method of making*", and also on the centralised European marketing authorisation EU/1/13/868, for the medicinal product "EVARREST"[2]. The marketing authorisation for EVARREST was granted following Commission Implementing Decision C(2013)6344 of 25 September 2013. As this is an authorisation granted under the centralised procedure by the European Medicine Agency (the "EMA"), it has to meet the requirements set down in Regulation (EC) 726/2004 (the "EMA Regulation") for a centralised approval that will cover all EU countries[3].

3 I note that the marketing authorisation for EVARREST was subsequently withdrawn by the European Commission at the request of the marketing authorisation holder

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[1] *This decision relates to a SPC that was applied for in 2014 and as such it is necessary to apply the relevant law that was in force at that time in the UK. This is set out in the decision below.*

[2] *EVARREST is a registered trademark (RTM) in the UK*

[3] *Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (see here)*

(MAH), Omrix Biopharmaceuticals N. V., on 15 November 2017[4]. The reason given by the MAH for its decision to "*permanently discontinue the marketing of the product in the EU*" was "*commercial reasons*". This MA was no longer valid after this date. However, when the application for the SPC was made, this MA was in force in the UK.

4 The product itself is identified on form SP1 accompanying the application as having the active ingredients "*thrombin, fibrinogen and oxidised regenerated cellulose*". Throughout the examination process, the examiner has maintained their view that of these three components, oxidized regenerated cellulose ("ORC") is just an excipient, and so cannot be considered to be an active ingredient within the meaning of Article 1(b) of Regulation (EC) No 469/2009 ('the SPC Regulation')[5]. This is because the examiner believes that, in applying the relevant case law as discussed below, neither the summary of product characteristics ("SmPC")[6,7] that accompanies the marketing

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[4] See public statement on withdrawal of the MA for EVARREST in the EU, dated 3 April 2018, on European Medicines Agency (EMA) website at EVARREST - Public statement (europa.eu).

[5] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the creation of a supplementary protection certificate for medicinal products is a codification of Council Regulation (EEC) 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products (the SPC regulation). Regulation (EC) 469/2009 supersedes Regulation (EEC) 1768/92 which had been amended substantially several times and codifies those changes. Annex II to Regulation 469/2009 indicates the correlation between the recitals and Articles in Regulation 1768/92 and those in Regulation 469/2009.

[6] SmPCs are the basis for the preparation of package leaflets for medicines, so are important documents in enabling information on medicines to reach patients. They describe the properties and the officially approved conditions of use of a medicine. They form the basis of information for healthcare professionals and patients on how to use the medicine safely and effectively. For details on how an SmPC is prepared, what it contains and how it is updated – see (i) SmPC : summary of product characteristics (europa.eu); and (ii) A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), September 2009, Revision 2 which is included in The Rules Governing Medicinal Products in the European Union, Volume 2C, Notice to Applicants at https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

[5] The SmPC is required by Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) 726/2004.

authorisation, nor the European Public Assessment Report ("EPAR")[8,9], make clear any pharmacological, immunological or metabolic effect of ORC in EVARREST.

5 In the examiner's opinion, as ORC is only referred to as an excipient, and owing to the absence of any mention in the SmPC and the EPAR of either a pharmacological, immunological or metabolic action of ORC, the medicinal product at issue should therefore be correctly identified as the combination of two active ingredients, namely thrombin and fibrinogen. This has the effect that a supplementary protection certificate cannot be granted in this case, as the application would not satisfy Article 3(d) of the Regulation, since the combination of just thrombin and fibrinogen has already been the subject of two earlier marketing authorisations: EU/1/04/277 and EU/1/08/473.

6 The applicants do not agree with the examiner's interpretation of Article 1(b), the relevant case law, or their assessment of the SmPC and EPAR. They argue that, in line with the case law, the determination as to whether ORC is an active ingredient should be made in light of ***all*** the facts. This has the consequence that, not just the SmPC and EPAR should be considered, but that it is appropriate, if necessary, to rely on evidence outside of these documents, such as that provided by the applicants in the present case, in order to show that ORC can be considered an active ingredient. Since there has been no earlier marketing authorisation for the triple combination of fibrinogen, thrombin, and ORC, they submit that the application should be allowed to proceed.

7 Following several rounds of correspondence, the matter came before me at a hearing on 23 November 2021, which took place by videoconference. At the hearing, the applicants were represented by their agents, David Holland and Rhodri Hopes, of Carpmaels & Ransford LLC. Senior Examiner Gareth Prothero acted as Hearing Assistant to the Hearing Officer.

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[8] A European public assessment report (EPAR) is published for every human (or veterinary) medicine application that has been granted or refused a marketing authorisation by the European Commission and is publicly available on the EMA website here. The EPAR is a set of documents describing the evaluation of a medicine authorised by the European Medicines Agency (EMA) via the centralised procedure. It comprises a series of documents and reports including: (i) a lay summary: (ii) details about the marketing authorisation holder; (iii) product information (such as the package leaflet and summary of product characteristics); and (iv) reports on the assessment carried out at EMA. It includes information on the medicinal product, the outcomes of the clinical trials and assesses the benefits and risks associated with this medicinal product. The reports on the assessment include the scientific conclusions of the relevant EMA committee, in this case, the Committee for Medicinal products for Human Use (CHMP), providing the grounds for the committee opinion to the European Commission on whether, or not, to approve an application. The EPAR is published following the assessment by EMA of an application submitted by a pharmaceutical company seeking authorisation of the medicinal product. EPARs are published on the EMA's website once the European Commission has issued a decision granting or refusing the marketing authorisation. The EPAR provides public information on a medicine, including whether it was assessed positively or negatively by EMA. For further information on purpose and contents see European public assessment reports: background and context | European Medicines Agency (europa.eu) and https://www.ema.europa.eu/en/ medicines/what-we-publish-when/european-public-assessment-reports-background-context.

[9] The EPAR is referred to in Article 13(3) of the EMA Regulation. This article requires the EMA to publish a public assessment report for each centrally authorised medicine together with a public-friendly overview.

The Basic Patent

8 The basic patent, EP(UK) 1809343 B1, entitled *"A reinforced absorbable multi-layered hemostatic wound dressing and method of making"*, was filed on 17 October 2005, with an earliest priority date of 20 October 2004, and it was granted on 15 August 2012. The expiry date of this patent is 16 October 2025.

9 The invention disclosed in this patent relates to a multi-layered wound dressing comprising (among other things) ORC, thrombin and fibrinogen. Paragraphs [0002] to [0005] of the patent set out the background to the invention and the desirability of keeping the ORC separate from the thrombin and fibrinogen components (my emphasis added in bold):

> *"[0002] The control of bleeding, as well as sealing of air and various bodily fluids, is essential and critical in surgical procedures to minimize blood loss, to seal tissue and organ structures, to reduce post-surgical complications, and to shorten the duration of the surgery in the operating room.*
>
> *[0003] In an effort to provide dressings with enhanced hemostatic and tissue sealing and adhering properties, therapeutic agents, including, but not limited to, thrombin, fibrin and fibrinogen have been combined with dressing carriers or substrates, including gelatin-based carriers, polysaccharide-based carriers, glycolic acid or lactic acid-based carriers and a collagen matrix. Examples of such dressings are disclosed in US-A-6,762,336, US-A-6,733,774 and WO-A-2004/064878.*
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> *[0004]* ***Due to its biodegradability and its bactericidal, tissue sealing, tissue repairing, drug delivering and hemostatic properties, it is desirable to utilize cellulose that has been oxidized to contain carboxylic acid moieties, hereinafter referred to as carboxylic-oxidized cellulose, as a topical dressing*** *in a variety of surgical procedures, including neurosurgery, abdominal surgery, cardiovascular surgery, thoracic surgery, head and neck surgery, pelvic surgery and skin and subcutaneous tissue procedures.*
>
> *[0005]* ***However, when carboxylic-oxidized cellulose is utilized in combination with thrombin and fibrinogen, the acidic moieties that may be present in the cellulose denature the activity of the thrombin and fibrinogen. Therefore, it is desirable to shield the thrombin and fibrinogen from such acid moieties to maintain their hemostatic activities."***

10 The product is protected by claims 1 to 4 of the basic patent which read as follows (my emphasis added in bold):

> *"1. A multilayered wound dressing comprising: a first layer of a first absorbable nonwoven fabric comprising fibers comprised of aliphatic polyester polymers or copolymers of one or more monomers selected from the group consisting of lactic acid, lactide (including L-, D-, meso and D, L mixtures), glycolic acid, glycolide, ε-caprolactone, p-dioxanone and trimethylene carbonate; and a second layer of* ***a second absorbable woven or knitted fabric comprising oxidised polysaccharides****, wherein said first absorbable nonwoven fabric contains thrombin and fibrinogen.*

2. The multilayered dressing of claim 1, where the first absorbable nonwoven fabric comprises glycolide/lactide copolymer.

3. The multilayered dressing of claim 1, where the ***second absorbable*** *woven or knitted* ***fabric comprises oxidized cellulose****.*

4. The multilayered dressing of claim 3, where the second absorbable woven or knitted fabric comprises ***oxidized regenerated cellulose****."*

The Issues to be Decided

11 Firstly, I need to consider whether the Regulation, and related case law, require that any pharmacological haemostatic effects of ORC must be indicated in the SmPC that accompanies the marketing authorisation, and/or in the EPAR; or, in the absence of such an indication, whether it is nevertheless possible to rely on other evidence of such pharmacological activity outside of these documents. For clarity I am considering pharmacological action only. There has been no suggestion or argument in this case that we are concerned with an immunological or metabolic action

12 Secondly, I will then need to consider the contents of the SmPC and EPAR for EVARREST, and, depending on my conclusion as to the first issue, the other evidence as put forward by the applicants, in order to decide whether ORC can be considered to be pharmacologically active. If I consider that ORC demonstrates a pharmacological action of its own, it can, thereby, be considered as an active ingredient. according to Article 1(b) of the SPC Regulation

13 There is no disagreement between the examiner and the applicants that if ORC is an active ingredient then a certificate can be granted for a medicinal product with three active ingredients, i.e., ORC, thrombin and fibrinogen.

14 Equally, there is no disagreement between the examiner and the applicants that, if my conclusion is that ORC is not an active ingredient then the present SPC application fails under Article 3(d) because earlier marketing authorisations already exist for the combination of thrombin and fibrinogen only.

The Relevant Law

15 Article 1 of the SPC Regulation defines various terms, of which Articles 1(a) and 1(b) are relevant to this decision and are reproduced below:

Article 1

Definitions

For the purposes of this Regulation, the following definitions apply:

(a) 'medicinal product' means any substance or combination of substances presented for treating or preventing disease in human beings or animals

and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;

(b) 'product' means the active ingredient or combination of active ingredients of a medicinal product;

(c) …

(d) ….

(e) ….

16 Article 3 of the SPC Regulation concerns the conditions for obtaining an SPC and reads as set out below. Part (d) of this Article states that a certificate cannot be obtained if the product has already been the subject of an earlier authorisation to place the product on the market (my emphasis added in bold):

Article 3

Conditions for obtaining a certificate

***A certificate shall be granted if**, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:*

(a) ….

(b) a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC or …..., as appropriate;

(c) …..

*(d) **the authorisation referred to in point (b) is the first authorisation to place the product on the market as a medicinal product**.*

17 Article 8 relates to content of the application for a certificate, and part (b) of this article reads as follows (my emphasis added in bold):

Article 8

Content of the application for a certificate

*1. **The application for a certificate shall contain:***

(a) ….

*(b) **a copy of the authorisation to place the product on the market**, as referred to in Article 3(b), in which the product is identified, containing in particular the number and date of the authorisation **and the summary of the product characteristics listed in Article 11 of Directive 2001/83/EC** or ……..;*

(c) *…..*

(d) *…..”*

18 As we are concerned with a medicinal product for human use in this case, for the purposes of Article 3 and Article 8, the authorisation provided in support of the SPC application at issue must be one granted under the Medicines Directive[10]. A number of procedures for authorisation of medicinal products for human use are possible under this Directive.

19 The EMA regulation (Regulation 726/2004/EC) set down the procedure for the authorisation, supervision and pharmacovigilance of medicinal products for human (and veterinary) use at the level of the European Community and established the European Medicines Agency (EMA) as the body responsible for delivering this procedure at Community level[3] – this is referred to as a centralised marketing authorisation. A marketing authorisation granted under this so-called centralised authorisation procedure is effective in all the members states of the European Union.

20 The EMA regulation sets out how the system for authorising medicinal products for human use in the European Union as set down in the Medicines Directive is applied to provide the option for a centralised authorisation that covers all countries in the European Union (EU).

Relevant Case Law

Court of Justice of the European Union (CJEU)

21 Two judgments from the Court of Justice of the European Union (CJEU) which refer to Article 1 and Article 3 of the SPC Regulation are relevant to the present case[11]. These are

(a) C-631/13, Arne Forsgren v. Österreichisches Patentamt (“*Forsgren*”)[12].

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*[10] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (the Medicines Directive). For consolidated text of directive see **here**. For details on how the authorisation system for medicines for human use in EU works - please see guidance form European Commission from July 2019 updated edition of Chapter 1: Marketing Authorisation, of Volume 2A: Procedures for Marketing Authorisation, in Volume 2: the Notice to Applicants of "The Rules governing Medicinal Products in the European Union” - see EudraLex - Volume 2 - Pharmaceutical legislation on notice to applicants and regulatory guidelines for medicinal products for human use | Public Health (europa.eu)*

[11] Given the legislative framework that was in place in the UK at the time when the application for the SPC was made in 2014 (i.e., prior to exit of the UK from the European Union in 2020), the decisions of the Court of Justice of the European Union (CJEU) had a binding effect on a lower tribunal in the UK, such as the IPO, in relation to interpretation of the SPC Regulation.

[12] For full text of the Forsgren CJEU decision see ECLI identifier ECLI:EU:C:2015:13 CURIA - Documents (europa.eu); EUR-Lex - 62013CJ0631 - EN - EUR-Lex (europa.eu)

(b) C-11/13, Bayer Crop Science AG v. Deutsches Patent- und Markenamt ("*Bayer*")[13].

22 I shall refer to the issues discussed in these judgments as necessary at the relevant points in the decision below.

UK Court

23 The most relevant UK authority is the following:

(c) *Abraxis Bioscience LLC v. The Comptroller-General of Patents* [2017] EWHC 14 (Pat) ("*Abraxis*")[14]

24 I shall refer to issues discussed in this judgment as necessary at the relevant points in the decision below.

The Relationship and Relevance of the Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR)

25 Before considering the issues at issue in the present case, it is helpful to be aware of the following details in relation to the how the centralised approval process works.

SmPC – Summary of Product Characteristics

26 In the countries of the European Union, medicines are granted a marketing authorisation by the European Commission so that they can be marketed and so made available for human use. The decision to grant the MA is dependent on a positive recommendation from the EMA to the European Commission. This recommendation is provided as a scientific opinion from the expert Committee for Medicinal Products for Human Use (CHMP) of the EMA which determines that there is a suitable risk v benefits profile for the medicinal product of interest and so recommends grant of the MA[15]. As part of this, the CHMP considers and approves the Summary of Products Characteristics (SmPC)[16] . The CHMP is made up of scientific experts from all EU member states and additional members with relevant expertise can be co-opted as necessary. The CHMP carries out a comprehensive scientific evaluation of the medicine based on the materials provided by the applicant and it can also ask for additional information from the applicant if necessary. It examines whether the medicine meets the necessary quality, safety and efficacy requirements as set down in Directive 2001/83/EC, the Medicines Directive, and determines if the medicine offers

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[13] For full text of the Bayer CJEU decision see ECLI identifier: ECLI:EU:C:2014:2010; CURIA - Documents (europa.eu); EUR-Lex - 62013CJ0011 - EN - EUR-Lex (europa.eu)

[14] For full text of the Abraxis decision from UK Patents Court see Abraxis Bioscience Llc v The Comptroller-General of Patents [2017] EWHC 14 (Pat) (13 January 2017) (bailii.org) (http://www.bailii.org/ew/cases/EWHC/Patents/2017/14.html).

[15] See also explanation in Footnote 6 above (on SmPC) and Footnote 8 above (re EPAR)

[16] As confirmed by Article 6(1) of Regulation 726/2004 (the EMA regulation), the requirements for preparation of the SmPC are those set down in Article 8(3) and related Annex 1 of Directive 2001/83/EC (the Medicines Directive)

a positive risk-benefit balance[17]. The European Commission decision to grant the marketing authorisation is based on this opinion – without a positive opinion from the CHMP, a marketing authorisation will not be granted.

27 The SmPC for EVARREST is referred to in Article 1 of Commission Implementing Decision C(2013)6344 granting the marketing authorisation for this medicinal product and is included as Annex I to this decision. The SmPC is drafted by the applicant and sets out the information for healthcare professionals on how to use the authorised medicinal product, and contains detailed essential information about the medicine including, among other things, its composition, dosage forms, therapeutic indications, and pharmacological details.[6,18] As has been noted above, the SmPC is approved and agreed by the CHMP as part of the assessment procedure used to produce the opinion and recommendation from the EMA to the European Commission on grant (or refusal) of the MA.[8]

EPAR - European Public Assessment Report

28 After grant of the MA by the European Commission, the EMA prepares and makes publicly available the European Public Assessment Report (EPAR) for the newly authorised medicinal product. The EPAR is produced from the scientific opinion prepared by the CHMP but it will have any commercially confidential information removed.

29 Although it is not formally part of the MA, the EPAR is derived directly from the full scientific assessment report produced by the CHMP for the EMA[8, 19]. The need for the EPAR and the role of the CHMP and EMA in delivering it are specified under Article 13(3) of the EMA Regulation[3,5]. The EPAR is not a single document but an information resource containing several components, including a core set of regulatory documents. The EPAR provides detailed information about the medicine including how the active ingredients work and its assessment history[4]. In addition, it also includes a public-friendly summary describing what the medicine is and what it does. This is presented in question-and-answer format. The package leaflet that will be distributed with the medicine is also included.

30 The EMA also makes publicly available information on those medicinal products that have been refused a marketing authorisation or, that have been suspended or withdrawn after being approved. As I have already noted above, the MA for EVARREST was withdrawn by the holder, Omrix Biopharmaceuticals Inc, within the first 5 years period after it was approved (see further discussion on this point below).

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[17] See EMA website for further details on the role of the CHMP - Committee for Medicinal Products for Human Use (CHMP) | European Medicines Agency (europa.eu).

[18] The SmPC is separate to the Labelling and Packaging Leaflet (attached as Annex III to Commission Implementing Decision C(2013)6344 and referred to in Article 3 of that decision) and to the Summary of conditions relating to manufacture, importation, control and issue (attached as Annex II to Commission Implementing Decision C(2013)6344 and referred to in Article 2 of that decision).

[19] See EMA website for further details on the procedure for centralised authorisation of medicines Authorisation of medicines | European Medicines Agency (europa.eu).

Analysis

31 In consideration of the first issue to be decided (see above), and before going on to look at the arguments from both sides, I think it is worth pointing out that the SPC Regulation itself does not provide any clear answer as to what extent the SmPC and/or the EPAR should be considered in order to determine whether a substance can be regarded an active ingredient within the meaning of Article 1(b). However, as set out above, I note that provision of a copy of the SmPC as well as of the authorisation itself is a requirement of Article 8(1)(b) of the Regulation, and it therefore forms an integral part of the SPC application process.

32 Turning now to consider the case law from the CJEU and UK courts that is helpful in determining what is an active ingredient for the purposes of the SPC regulation, I will consider the *Forsgren* and *Abraxis* cases.

Forsgren, C-631/13

33 The applicants argue that the examiner has applied the wrong legal test by using what the applicants call an "SmPC/EPAR-only approach" in determining the question of whether ORC is an active ingredient. In this regard, they assert that such an approach was dismissed by the Court of Justice of the European Union (the "CJEU"), in *Arne Forsgren v. Österreichisches Patentamt*, case C-631/13 ("*Forsgren*").

34 This decision resulted from a referral by the Austrian Oberster Patent- und Markensenat to the CJEU following the refusal of Mr Forsgren's application for a supplementary protection certificate for Protein D. The marketing authorisation relied upon related to the medicinal product 'Synflorix', a vaccine composed of ten pneumococcal polysaccharide serotypes conjugated to carrier proteins. In eight of the ten serotypes Protein D was the carrier protein.

35 Three questions were considered by the court:

(1) is grant of an SPC precluded on the sole ground that the active ingredient is covalently bound to other active ingredients?

(2) (a) whether grant of an SPC is precluded for an active ingredient whose therapeutic effect does not fall within the therapeutic indications covered by the wording of the marketing authorisation; and

(2) (b) whether a carrier protein conjugated to a pneumococcal polysaccharide used in a vaccine for a paediatric use may be regarded as a 'product' within the meaning of the Regulation, i.e. as an active ingredient or combination of active ingredients.

36 At the hearing, Mr Holland argued that it is question (2)(b) that is the most relevant to the present situation. In particular, he pointed towards paragraphs 53 and 54 of *Forsgren*, reproduced below:

> *"53. In the light of the wording and purpose of Regulation No 469/2009, it must be held that Article 1(b) of that regulation does not permit an 'active ingredient' to be categorised as a carrier protein conjugated with a polysaccharide antigen by means of a covalent binding, unless it is established that it produces a*

pharmacological, immunological or metabolic action of its own. Ultimately, it is for the referring court to determine, in the light of all the facts of the dispute on which it is required to rule, whether, on the basis of those criteria, Protein D, conjugated with pneumococcal polysaccharides which form part of Synflorix, produces a pharmacological, immunological or metabolic action of its own, and whether that effect falls within the therapeutic indications covered by the wording of the marketing authorisation.

54. In view of all the foregoing, the answer to Question 2(b) is that Article 1(b) of Regulation No 469/2009 must be interpreted as meaning that a carrier protein conjugated with a polysaccharide antigen by means of a covalent binding may be categorised as an 'active ingredient' within the meaning of that provision only if it is established that it produces a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indications of the marketing authorisation, a matter which it is for the referring court to determine, in the light of all the facts of the dispute in the main proceedings."

37 In view of these passages, the applicants argue that the CJEU decided that a substance can be considered an 'active ingredient' under Article 1(b) "*only if it is established that it produces a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indications of the marketing authorisation, a matter which it is for the referring court to determine, in the light of all the facts of the dispute in the main proceedings*" (emphasis added).

38 The applicants take this reference to 'in light of all the facts' at paragraphs 53 and 54 as a direction that assessment of the active ingredient should not be regarded as restricted to just the SmPC and EPAR, but should be established based on all the evidence, including evidence outside of the SmPC and EPAR. At the hearing, Mr. Holland suggested that this should involve "a broad factual enquiry". In the applicants' view, had the CJEU wanted to establish an SmPC/EPAR-only approach it could have done so.

39 Furthermore, the applicants also point out that paragraph 31 of *Forsgren* indicates that the European Commission had argued that evidence outside of the marketing authorisation should not be taken into account in considering whether a substance could be considered an active ingredient, but that the CJEU did not take the opportunity to endorse this view. Paragraph 31 is reproduced below:

"31. The European Commission contends that, in order for an SPC to be granted, the marketing authorisation procedure for the product covered by the basic patent must have been successfully completed. In the absence of such a marketing authorisation, there is no reason for an extension of the term of the protection conferred by the patent. The Commission adds that the system established under Regulation No 469/2009 is intended to establish some simplicity and some transparency. That objective would not be achieved if the competent authority were required to verify by reference to sources other than the marketing authorisation whether the substance at issue is an active ingredient."

40 Having carefully considered *Forsgren*, especially the paragraphs highlighted by the applicants, I accept their point that whether a substance produces a pharmacological, immunological or metabolic action of its own needs to be determined in light of all the facts. However, I do not agree that an '*all the facts'* enquiry should be taken so far as allowing for the consideration of evidence of such an effect if the marketing

authorisation, including the SmPC, and the EPAR, is completely silent on the issue. In particular, I note that, in answering question 2(b), the CJEU specifically considered the contents of the EPAR for Synflorix, and came to the conclusion that, while unconjugated polysaccharide vaccines do not induce an immunogenic response and memory in children under two years old, polysaccharide antigens conjugated with a carrier protein (which included those conjugated to Protein D) did induce such effects. Paragraphs 47 and 48 are reproduced below:

> *"47. In that regard, it follows from paragraph 25 above that the term 'active ingredient', for the purposes of applying Regulation No 469/2009, relates to substances which produce a pharmacological, immunological or metabolic action of their own. It is thus apparent from the introduction to the European Public Assessment Report that unconjugated polysaccharide vaccines are not appropriate for the purpose of inducing an immunogenic response and memory in children of less than two years. On the other hand, according to the same report, where polysaccharide antigens are conjugated with a carrier protein, they may induce such effects.*
>
> *48. In the light of those considerations, it is appropriate to establish whether a carrier protein used in a medicinal product, which does not have an immunogenic effect of its own that is covered by the wording of the marketing authorisation, may be categorised as an 'active ingredient' where, conjugated with a polysaccharide antigen by means of a covalent binding, it produces such an effect."*

41 Since it showed that a carrier protein, when conjugated with a polysaccharide antigen, may induce an immunogenic response (even though it did not show that the carrier proteins on their own showed such a response), the EPAR for Synflorix did at least provide the basis for the possibility that protein D could induce an immunological response of its own, and it seems to me that the CJEU decided that in those circumstances it was appropriate for the referring court to determine, in light of all the facts, whether this was indeed the case. This, in my view, is not the same as allowing the consideration of evidence further to the SmPC and/or EPAR in the event that those documents are completely silent that a substance has a pharmacological, immunological or metabolic effect of its own.

42 With regard to paragraph 31, in my opinion this amounts to no more than a summary of the European Commission's argument that the objectives of the Regulation would not be achieved were the competent authority required to determine whether a substance is an active ingredient by reference to sources other than the marketing authorisation. The court does not go on to either explicitly confirm or reject such an approach. I also note that this paragraph relates to Question 2(a) of the decision, which was in fact specifically answered by the court with regard to both the SmPC and the EPAR (see paragraphs 37 to 39 of the *Forsgren* judgment). In particular, as neither the SmPC nor the EPAR contained any trial data concerning the therapeutic effects of Protein D against *Haemophilus Influenzae*, the marketing authorisation procedure thus did not result in a delay to the use of the basic patent, and that in such circumstances, the grant of an SPC is precluded.

UK Patents Court - Abraxis decision

43 The examiner relies upon the decision in *Abraxis Bioscience LLC v. The Comptroller-General of Patents* [2017] EWHC 14 (Pat) ("*Abraxis*") as the basis for his approach regarding the consideration of the SmPC and the EPAR. This decision of the High Court concerned an appeal by *Abraxis* following the refusal by the UK Intellectual Property Office of its SPC application for a product described as "*paclitaxel formulated as albumin bound nanoparticles*", on the grounds that it did not comply with Article 3(d) of the SPC Regulation. Paclitaxel itself had already been the subject of previous marketing authorisations. In particular, the examiner relies upon the words of Arnold J at paragraph 59, where he stated:

> *"59. Fourthly, it is clear from Forsgren that, consistently with Article 8(1)(b) of the SPC Regulation, when considering whether a substance produces a pharmacological, immunological or metabolic effect of its own so as to constitute an active ingredient, it is proper to refer to both the SmPC forming part of, and the EPAR which led to, the marketing authorisation which covers that substance. (In this respect, the position adopted by the CJEU with respect to the SPC Regulation differs from that adopted by it with respect of European Parliament and Council Regulation 1610/96/EC of 23 July 1996 concerning the creation of a supplementary protection certificate for plant protection products in Case C-258/99 BASF AG v Bureau voor de Industriële Eigendom [2001] ECR I-3643 at [31].) As the Comptroller contends, in the present case, the SmPC and EPAR for Abraxane both make it plain that the active ingredient of Abraxane is paclitaxel and that what Abraxis calls nab-paclitaxel is a formulation of paclitaxel. This supports the hearing officer's findings of fact. I should make it clear that, in saying this, I am not ruling upon the Comptroller's contention advanced by way of respondent's notice that the hearing officer should have confined himself solely to what was stated in the marketing authorisation (and possibly the EPAR), since it is not necessary for me to do so."*

44 The examiner is therefore of the opinion that, in accordance with the words of Arnold J, it is proper to refer to the SmPC and, if necessary, the EPAR, to determine whether a substance is an active ingredient. Doing so leads the examiner to the conclusion that ORC cannot be regarded as an active ingredient under Article 1(b).

45 The applicants, on the other hand, argue that Arnold J did not state explicitly, in the above paragraph relied upon by the examiner, that only the SmPC and/or EPAR can be considered when deciding whether a substance produces a pharmacological, immunological or metabolic effect of its own. They also refer to paragraphs 57 and 58 of *Abraxis*, reproduced below, as giving context to what is stated at paragraph 59:

> *"57. Secondly, it is clear from Forsgren that an active ingredient is a substance which produces a pharmacological, immunological or metabolic effect of its own.*
>
> *58. Thirdly, the hearing officer found as facts that (i) nab-paclitaxel is not a single active ingredient, (ii) the active ingredient in nab-paclitaxel is paclitaxel and (iii) the albumin functions as a carrier which is not covalently bonded to the paclitaxel. As counsel for Abraxis expressly confirmed, Abraxis does not challenge the hearing officer's findings of fact. Abraxis argues that the hearing officer incorrectly interpreted Article 1(b), but his application of the law was based on his findings of fact."*

46 With reference to paragraph 58, the applicants note that, in the decision of the Intellectual Property Office[20] that gave rise to the appeal in *Abraxis*, the hearing officer had considered a range of evidence other than the SmPC and the EPAR, and that he did not suggest that only the SmPC and EPAR should be considered. In their view, the hearing officer therefore made his decision about the active ingredient based on all the evidence. This, according to the applicants, has the effect that the 'fourthly' point made at paragraph 59 of *Abraxis* merely states that the SmPC and EPAR can be referred to, but consideration should not be restricted only to these documents, and this would in any case be inconsistent with *Forsgren*.

47 I do not fully agree with the applicant's arguments on this point. Although I accept their submission that Arnold J did not explicitly state that only the SmPC and EPAR should be referred to, the use of the word 'proper' in paragraph 59 of *Abraxis* ("….*it is proper to refer to both the SmPC forming part of, and the EPAR….")* suggests, in my view, more than a consideration of the SmPC and EPAR *among other things*, which I think is the upshot of the applicants' position. I think that Arnold J meant that it is *correct* to refer to these documents, from which it can be inferred that it would be incorrect, or improper, not to refer to them. This view is reinforced by the judge's specific reference to Article 8(1)(b) of the Regulation, which as I have noted above, requires the inclusion of the SmPC in the SPC application. In light of this, I find it difficult to conclude that, if the SmPC and/or EPAR are silent as to any pharmacological, immunological or metabolic effect of a purported active ingredient, then it is nevertheless appropriate to consider evidence outside of the marketing authorisation in order to answer the question. In my view, the pharmacological, immunological or metabolic effect of each active ingredient must = at least be made clear from the SmPC and/or EPAR. This, in my view, is an "SmPC/EPAR-led" approach and not an "SmPC/EPAR-only" approach as characterised by the applicant. Furthermore, I should add that I consider my conclusion in this regard is entirely consistent with those above with respect to *Forsgren*. I do not think that the fact that the hearing officer's decision under appeal in *Abraxis* considered other documentary evidence affects the situation here, because the hearing officer nevertheless also considered the contents of the SmPC[21].

48 It is also the case that the approach taken by the hearing officer in relation to the *Abraxis* case before the IPO is not binding upon me. Although I can draw comparison with and support from other office decisions, only the decisions of the Patents Court and the higher courts are binding on me[22].

Bayer, C-11/13

49 The applicants argued that the SmPC is not governed or regulated by the SPC Regulation. They consider that the CJEU held in *Bayer CropScience AG v. Deutsches Patent- und Markenamt*, case C-11/13 ("Bayer"), that the SPC system is governed independently of other related legislation. Although this case related to the SPC

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[20] See IPO decision BL O/410/16 (Abraxis) here

[21] See Footnote 20; see paragraphs 35 to 41, 62, 88, 91, and 105 of BL O/410/16 (Abraxis)

[22] The UK Patents Court, the UK Court of Appeal, the UK Supreme Court and, up to December 2021, the Court of Justice of the European Union

regulation for plant protection products[23], they consider that it applies by analogy and by virtue of the link established by Recital 17 of the plant protection product SPC regulation equally to the SPC regulation for medicinal products, EC Regulation 469/2009. The applicants point towards paragraph 42 of Bayer decision, where the court endorsed the view of the Advocate General (at paragraph 39 of his Opinion) that "*the grant of a supplementary protection certificate remains governed independently by Regulation 1610/96*". Paragraph 39 of the Opinion, and paragraph 42 of the decision, are reproduced below respectively[24]:

> *(from Opinion of CJEU, Bayer)" "*
>
> *39. It must therefore be concluded that Directive 91/414 is not without importance for the application of Regulation No 1610/96 in general. The objective of that regulation is, precisely, to encourage innovations in products which satisfy the conditions laid down in Directive 91/414 and which have been granted an MA. In my view, however, the grant of a supplementary protection certificate remains separately regulated by Regulation No 1610/96*
>
> …..
>
> *(from Judgment of CJEU, Bayer)"*
>
> *"42. However, as the Advocate General noted in point 39 of his Opinion, while Directive 91/414 is not without importance for the application of Regulation No 1610/96, the grant of a supplementary protection certificate is still regulated autonomously by that regulation. Thus, although no safener was included in Annex I to Directive 91/414 as an active substance, that fact does not lead to the definitive conclusion that the commercial exploitation of a patent for a safener has not been delayed on account of the time required to obtain an MA 'in accordance with Article 4 of Directive [91/414] or an equivalent provision of national law' within the meaning of Article 3 of Regulation No 1610/96.*

50 I accept the applicants' argument that it has to be borne in mind that the marketing authorisation, including the SmPC, is not created solely for the purposes of the SPC Regulation. The SPC system can be considered as autonomous, as set out in *Bayer*. However, it still seems to me entirely appropriate and necessary, in the autonomous application of the SPC Regulation, to draw upon the provisions of closely related legislation, particularly when it is referred to directly as part of the SPC Regulation. In that respect, the Medicines Directive is specifically referred to and incorporated into Articles 2, 3, 8 and 14 of the SPC Regulation. Furthermore, terms such as summary of product characteristics are included in the SPC Regulation but are defined in Directive 2001/83/EC. The interpretation of Article 1(b), as set out in *Forsgren*, and as submitted in the applicants' own arguments, also draws directly upon the wording as set out in Article 1 of the Medicines Directive (Directive 2001/83/EC).

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[23] Regulation (EC) No 1610/96 of the European Parliament and of the Council of 23 July 1996 concerning the creation of a supplementary protection certificate for plant protection products

[24] Directive 91/414/EC of 15 July 1991 concerning the placing of plant protection products on the market. This directive has now been replaced and superseded by Regulation (EC) 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EC.

51 Paragraphs 24 and 25 of *Forsgren* specifically refer to the wording of Directive 2001/83, and are set out below:

> *"24. That interpretation was subsequently reproduced, in essence, by the EU legislature. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 (OJ 2011 L 174, p. 74) amended Article 1 of Directive 2001/83 to the effect that the term 'active substance' — which must be understood as meaning 'active ingredient' (judgment in Massachusetts Institute of Technology,EU:C:2006:291, paragraph 21) — is defined therein as 'any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis'.*
>
> *25. It follows that the term 'active ingredient', for the purposes of applying Regulation No 469/2009, concerns substances producing a pharmacological, immunological or metabolic action of their own. Since Regulation No 469/2009 does not draw any distinction according to whether an active ingredient is covalently bound with other substances, it is not appropriate to exclude, on that ground, the grant of an SPC for such an active ingredient."*

52 In view of the fact that the CJEU has concluded that the scope of the term 'active ingredient' should be aligned closely with that used to define the term 'active substance' in Directive 2001/83, this makes it very difficult to see how the effects of Directive 2001/83 can be entirely removed from all consideration of the SPC Regulation. By way of confirmation, such an approach would also be at odds with the decision of the CJEU in *GlaxoSmithKline Biologicals SA and GlaxoSmithKline Biologicals, Niederlassung der SmithKline Beecham Pharma GmbH & Co., KG v Comptroller General of Patents, Designs and Trade Marks*, Case C-210/13, referred to by the examiner in his pre-hearing report. The CJEU in this decision deliberately drew upon the distinct concepts of 'adjuvant' and 'active substance' in Directive 2001/83 in coming to the conclusion that an adjuvant cannot be considered an active substance within the meaning of the SPC Regulation. Paragraph 38 is reproduced below:

> *"38. Thus, in Directive 2001/83, as amended by Directive 2003/63, the concepts of 'active substance' and 'adjuvant' are clearly distinct and that also holds, in the context of Regulation No 469/2009, for the concept of 'active ingredient', which cannot, as such, include an adjuvant."*

Although in *Bayer*, the court found that a safener could be included in the meaning of as an active substance, I note that the plant protection authorisation regulation provides the meaning of these terms and how they are understood. There is not a straightforward or direct read across between active ingredient in the medicinal product authorised under Directive 2001/83/EC and the safeners in plant protection products authorised under Directive 91/414/EC, or its successor Regulation (EC) 1107/2009,[24] for use as plant protection products. It was necessary in the view of the court in Bayer to consider what was the involvement of the safener added in with the active substance to achieve a particular plant protection outcome of interest. However, what is key here is to establish that the safener is actually subject to the same assessment process as the active substance in the plant protection product been investigated.

The Manual of Patent Practice

53 The applicants also refer to the Office's Manual of Patent Practice at paragraph SPM 1.04.2, which states that:

> *"In order to determine which components of a medicinal product are active ingredients and which are not this Office may refer to the summary of product characteristics and (if available and applicable) European public assessment reports as well as other evidence compiled by the applicant. This practice was approved of in Abraxis Bioscience LLC v Comptroller General of Patents [2017] EWHC 14 (Pat)."*

54 Again, in my opinion this does not amount to a statement that it is possible to rely upon *any* evidence, in the absence of any in the SmPC and/or the EPAR, in order to show that a substance forming the basis of an SPC application is an active ingredient. This paragraph refers to the UK court decision in *Abraxis*, which I have already considered above, where the additional evidence compiled by the applicant was used to explore what was the role of the albumin component, i.e. the albumin improved how the active ingredient paclitaxel was able to get to the part of the body that required cancer therapy. The albumin had no direct therapeutic effect of its own and so did not meet the requirement of an active ingredient under Article 1(b) of the SPC Regulation.

Decision of the Spanish Court in Halozyme case

55 The applicants have further drawn my attention towards a decision of the High Court of Justice of Madrid, Spain, in *Halozyme, Inc. v la Oficina Española de Patentes y Marcas, Appeal No. 256/2019, Judgment No. 696* ("*Halozyme*"), in which the appellant successfully appealed the decision of the Spanish Patent and Trademark Office to refuse its SPC application for the combination of trastuzumab and recombinant human hyaluronidase. The applicants argue that the first paragraph at page 12 of the machine translation of the decision (as supplied by the applicants) indicates that the Spanish Patent and Trademark Office refused the SPC application on the grounds that recombinant human hyaluronidase was only mentioned as an excipient in the SmPC for Herceptin, and that experimental evidence cited in a report was not considered. On appeal to the High Court of Justice of Madrid it was accepted that, on the basis of expert evidence showing the therapeutic effects of recombinant hyaluronidase, recombinant human hyaluronidase could be considered an active ingredient, and that a certificate could be granted.

56 Having considered this decision, and while I accept it has parallels with the decision before me, I can find nothing that alters my analysis as set out above. In particular, and as acknowledged by the applicants, this decision is not binding upon me. Furthermore, the Spanish High Court, of course, was not bound by the decision of the UK courts in *Abraxis*, which makes specific reference to use of the SmPC and EPAR. As the lower tribunal, the Office has to take account of UK court decisions

57 In any case, other than referring to *Forsgren*, the precise reasoning given by the Spanish court for accepting external evidence aside from the SmPC and EPAR is not entirely clear from the machine translation of this decision, and so appears to shed little light on the matters before me.

58 I note also that it would appear that in the corresponding proceedings in France the court came to the opposite conclusion to the High Court of Madrid, in finding that recombinant hyaluronidase is not an active ingredient in the medicinal product[25,26]. As a result, I do not consider that the outcome from these judgments are helpful in the present case.

Conclusion regarding the first issue to be decided

59 Having considered the Regulation and the relevant case law, I conclude that, in line with *Forsgren* and *Abraxis*, in order for a substance to be considered an active ingredient, it is necessary that the SmPC and/or the EPAR must contain, at the very least, some indication that the substance gives rise to a pharmacological, immunological or metabolic effect of its own. Therefore, in the present situation, it must be apparent from the SmPC and/or EPAR for EVARREST that ORC has a pharmacological effect of its own in haemostasis, in order for it to be considered an active ingredient within the meaning of Article 1(b). Given that the term haemostat is used to cover both passive haemostasis which is a physical effect and active haemostasis which is a pharmacological effect, I consider that there needs to be evidence of the latter in the SmPC and EPAR. To be clear, in the absence of any such indication, I do not think it is possible to rely upon evidence outside of the SmPC and/or EPAR, in order to show that this is the case. Thus, I think it is possible for evidence from other sources to be used to supplement or offer additional material to that disclosed in the SmPC and EPAR. However, if there is nothing on the issue in the SmPC or in the EPAR, I do not consider that evidence from other sources can be used to establish that one component in the medicinal product can be considered as an active ingredient. The SmPC and the EPAR which are based on the same materials relate to matters that were investigated to establish that the medicinal product in question had a suitable risk-v-benefit profile, thus this discussion needs to include information on what is (are) the active substance(s) in the medicinal product and how it (they) exert their pharmacological, immunological or metabolic action. I am satisfied that evidence from other materials can be considered to supplement the information provided in the SmPC and its related EPAR but not, to in effect, provide information for which there is no basis in the SmPC and EPAR. As I have referred to above, I consider that this is an 'SmPC-EPAR-led' approach and not an 'SmPC-EPAR-only' approach.

Haemostasis and the role of ORC

60 The examiner does not disagree with the applicants when they state that it is known in the art that ORC can play a pharmacological role in haemostasis. However, where the disagreement lies is in relation to whether there is a clear indication in the SmPC or the EPAR that ORC is playing more than a physical role in the therapeutic activity

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[25] *Halozyme Inc v. Directeur Général de l'INPI, Paris Court of Appeal (18/14332).*

[26] *So far as I have been able to establish, litigation on this case has been proceeding in a number of jurisdictions in Europe – in addition to the decision from the Spanish and French courts referred to above, the courts in Sweden upheld the national office decision not to grant the SPC was supported and approved; the courts in Portugal upheld the national office decision at first instance to refuse but this was overturned on appeal.*

achieved by the medicinal product. Before I consider the SmPC and the EPAR for the EVARREST medicinal product, I will consider the further evidence provided by the applicants in support of their view that ORC is playing a pharmacological role in haemostasis. The agent, Mr Hopes, took me through these points at the hearing. I have summarised these below:

- EP 1809343 B2 (the basic patent)
- US 3364200 A
- Cellulose, 2012, Hutchison R.W. et al., "Hemostatic efficacy and tissue reaction of oxidized regenerated cellulose hemostat" ("*Hutchison*").
- Resnik R.R., "Intraoperative Complications: Bleeding, Chapter 7. ("*Resnik*")
- Cellulose, Vol. 20, 2013, Cheng W. et al., "Preparation and characterization of oxidized regenerated cellulose film for hemostasis and the effect of blood on its surface", pp. 2547-2558. ("*Cheng*")
- Schonauer C. et al., "The use of local agents: bone wax, gelatin, collagen, oxidized cellulose". ("*Schonauer*")

61 For the avoidance of doubt, I take the term 'haemostasis' to refer to the "ability to control and/or ablate capillary, venous, or arteriole bleeding within an effective time", as defined at paragraph [0011] of the basic patent. Furthermore, I take the term 'haemostat' as relating to any material that promotes haemostasis. It is also clear that the term haemostat is used to refer to something which exerts it effect through physical means – this is also referred to as a passive haemostat - and also to something which exerts its effect through pharmacological means – this is also referred to as an active haemostat

62 While I do not think it is necessary for me to reproduce here in detail all of the documents provided as evidence by the applicants, I have highlighted some relevant passages below to illustrate their general theme.

63 *Schonauer*, states that (under the heading 'Historical background', at page 89):

> *"In the event of haemorrhage, hemostasis is naturally carried out by vasal constriction, platelets, coagulation factors and blood flow. Sometimes, during an operation, it is not possible to wait for the natural hemostatic process to occur, and, therefore, additive methods to obtain a stable coagulum have to be used. ….*
>
> *In general, these methods fall into one of the above three basic categories: thermal, mechanical, or chemical means….."*

64 This document also suggests, at page 91 (third paragraph) that ORC is involved in multiple mechanisms of action without explicitly identifying what they are:

> *"…ORC presents multiple mechanisms of action, including physical and mechanical actions in tamponade, food absorption, swelling and gel formation, and then surface interactions with proteins, platelets, intrinsic and extrinsic pathway activation.*

65 I also consider that the first paragraph of the Introduction of Cheng (in the paragraph bridging pages 2547 and 2548) as being relevant here where it indicates the difference between an active haemostat and a passive haemostat (my emphasis added in underline):

> *"Advances in technology have led to various ways of conducting hemostasis in surgery; one popular method is applying local hemostatic materials to the bleeding site. In cases of low bleeding, active hemostat that directly engaged* [sic] *in blood coagulation is used, such as thrombin and fibrin sealant; in cases of large bleeding, passive hemostat that can absorb blood multiple times as much as its own mass is used, such as collagen, oxidized regenerated cellulose and gelatin……"*

66 At the hearing, Mr Hopes also drew my attention to the second paragraph at page 2556 of *Cheng*, which discloses results of an animal model of bleeding, and which indicates that ORC has a strong activation on the platelets. I note that this document further states (in the passage bridging the left- and right-hand columns at page 2556):

> *"A kind of probable hemostasis mechanism is shown in Scheme 2. The hemostatic mechanism of ORC film probably is a combination of physical adsorption and the physiological hemostasis. When the ORC film is applied to the bleeding wound, because of the excellent wettability on the surface, the ORC could absorb most of the liquid in the blood, it also accelerates the concentration of blood. Afterwards, the carboxyl on the surface is exposed and carries electric charge which could rapidly attract and activate the platelets. After platelets activation, the platelet glycoprotein (GPIIb/IIIa) receptor becomes competent to bind soluble fibrinogen, which bridges GPIIB/IIIA between adjacent platelets, and this could stimulate the release of cellular grain and secretion, including all sorts of clotting factors which are able to adhere on the damaged blood vessels to fill the damaged organization and stop bleeding."*

67 I therefore agree with both the applicants and the examiner that evidence external to both the SmPC and EPAR exists that ORC acts as a haemostat in a physical (or passive) manner and that it may also act as a haemostat in a pharmacological (or active) sense. However, following my analysis of the case law above, the question remains: do the SmPC and the EPAR for EVARREST themselves suggest that ORC has a pharmacological effect of its own, or do they mention only a physical (i.e., non-pharmacological) role only?

Role of ORC discussed in SmPC and the EPAR

SmPC

68 The examiner is of the opinion that there is no reference to any pharmacological effect in either of these documents. With regard to the SmPC, the examiner relies in particular upon the second paragraph of section 5.1, which states (my emphasis added as underline):

> *"The composite Matrix is composed of polyglactin 910 and oxidized regenerated cellulose, a commonly used haemostat. The Matrix provides physical support and a large surface area for the biological components, imparts inherent mechanical integrity to the product and supports clot formation. The clot formation of EVARREST is integrated with the Matrix; it forms a mechanical barrier to bleeding and reinforces the wound site. Natural healing occurs while the fibrin degrades*

and the product is absorbed by the body; absorption is considered to take approximately 8 weeks, as demonstrated in rodent and swine animal models".

69 On the other hand, the applicants argue, at paragraph 3.2 of their skeleton arguments, that the above passage of the SmPC is evidence that ORC has a pharmacological effect, in view of the reference that the matrix "*supports clot formation*". In their opinion, this reference to supporting clot formation, in combination with other evidence they have provided as outlined above, shows that ORC has a pharmacological effect.

70 At the hearing, Mr Hopes also pointed towards the reference in this passage that ORC is a commonly used haemostat. However, while I acknowledge that this passage refers to regenerated cellulose being a haemostat, as I have noted above, this term alone does not necessarily refer to pharmacological haemostatic effects only, and so needs to be put in context. To me, what this passage is saying, is that ORC, in combination with the polyglactin, forms a "*physical support*" for the biological components (i.e., thrombin and fibrinogen). The ORC is therefore acting as a haemostat in the physical sense only. Clot formation is supported by the matrix because it is physically present, providing a barrier to cover the wound site and provide a means to support the active ingredients and bring them into close physical contact with the blood from the wound where they can then react with the blood and promote formation of a clot which results from the presence of the fibrinogen and the thrombin. Therefore, in contrast to the view of the applicants, I consider that this passage does not refer to an active role of ORC itself in clot formation, and so does not in fact support their view that ORC is playing a pharmacological role within the EVARREST product.

71 I further note that in the preceding paragraph of section 5.1, it is stated (my emphasis added in underline):

"EVARREST contains Human Fibrinogen and Human Thrombin as a dried coating on the surface of an absorbable composite Matrix. In contact with physiological fluids, e.g., blood, lymph, or physiological saline, the components of the coating are activated, and the reaction of fibrinogen and thrombin initiates the last phase of physiological blood coagulation. Fibrinogen is converted into fibrin monomers which spontaneously polymerise to form a fibrin clot that holds the Matrix firmly to the wound surface. The fibrin is then cross-linked by endogenous Factor XIII, creating a firm, mechanically stable fibrin network with good adhesive properties."

72 It also seems very clear from this passage that the matrix acts as an absorbent, and that it is the thrombin and fibrinogen that are activated on contact with blood to initiate physiological blood coagulation. There is no mention here of any activation of ORC in this process.

73 I also note that section 6.1 of the SmPC lists the composite matrix (comprising polyglactin 910 and ORC), as an excipient, which clearly leads away from the conclusion that the presence of ORC gives rise to a pharmacological effect.

74 To summarise the above points, I can find nothing in the SmPC to support the view that ORC has a pharmacological effect in haemostasis arising through use of the EVARREST product.

EPAR

75 Turning now to the EPAR, the examiner has noted the following passages:

- (Page 1)

  "Assessment report

  EVARREST

  Common name: Human Fibrinogen / Human Thrombin"

- (Section 2.1.; "Introduction", third paragraph, at page 7)

  "EVARREST is a sterile bio-absorbable combination product made from a composite matrix coated with fibrinogen and thrombin. It is presented as a sealant matrix, which combines two haemostatically active components: a flexible matrix consisting of polyglactin 910 (PG910) filaments needle punched into a backing fabric of oxidized regenerated cellulose (ORC), and a coating of two biological components, human fibrinogen and human thrombin. Polyglactin is contained in surgical products like suture or mesh material and oxidized regenerated cellulose is widely used during surgery as a topical absorbable haemostat. The biological components are manufactured from normal human plasma and are identical to those used in the manufacture of the approved product Evicel as "solutions for sealant" by the same MAH. Upon contact with blood or fluid, the biological components hydrate and react by generation of fibrin. The matrix holds the fibrin clot at the site of bleeding and additionally offers a texture for blood components in order to support local haemostasis".

- (Section 2.2.3.; "Finished Medicinal Product"; first and second paragraphs, at page 11)

  "EVARREST sealant matrix is a sterile bio-absorbable haemostatic medicinal product made from a flexible matrix component coated with Human Fibrinogen and Human Thrombin active substances.

  The composite matrix is regarded to be a novel excipient in the production process of EVARREST and forms an integral part of the final drug product. The Matrix is manufactured by a contract manufacturer. A full quality dossier regarding the matrix has been provided."

- (Section 2.2.3.; "Pharmaceutical Development", first paragraph, at page 11)

  "Formulation development was aimed at optimizing physicochemical properties of carrier material in order to make it capable of controlling challenging bleeding while containing moderate concentrations of biological drug substances, at optimizing the target input dose of fibrinogen and at establishing the dose for commercial product".

- (Section 2.2.4.; "Discussion on chemical, pharmaceutical and biological aspects", first paragraph, at page 14)

  "The active ingredients of EVARREST Sealant matrix (Human Fibrinogen and Human Thrombin) are two known active substances, being the drug substances of the centrally approved fibrin sealant EVICEL manufactured by OMRIX".

76 At the hearing, Mr Hopes also pointed me towards the following passages of the EPAR as supporting their position as to the pharmacological (or active) role of ORC:

- (Section 2.1.; "Introduction", first paragraph, at page 6)

  "….Topical haemostatic agents (gelatine, collagen, or oxidized regenerated cellulose) are widely used as an adjunct to these methods. …."

- (Section 2.1.; "Introduction", third paragraph, at page 7)

  "….It is presented as a sealant matrix, which combines two haemostatically active components: a flexible matrix consisting of polyglactin 910 (PG910) filaments needle punched into a backing fabric of oxidized regenerated cellulose (ORC), and a coating of two biological components, human fibrinogen and thrombin. …."

- (Section 2.5.3.; "Design and conduct of clinical studies", first paragraph, at page 67)

  "….Three prospective, randomized, and controlled studies versus Surgicel , an oxidised regenerated cellulose (ORC) product widely used in surgery as a haemostatic product (Study 400-07-002) or versus the surgeon's routine Standard of Care (400-08-002 and 400-010-001), were submitted. …."

- (Section 2.5.3.; "Efficacy data and additional analyses", second paragraph, at page 68)

  "….While the oxidized regenerated cellulose product Surgicel had quite acceptable haemostatic efficacy in mild bleedings, defined as a small area of capillary, arteriole or venule oozing, treatment failures became frequent in the attempt to stop moderate bleedings with Surgicel . …."

77 I understand Mr. Hopes' point as being that the above passages of the EPAR allude to the haemostatic efficacy of ORC, from which starting point one can move on to look at the other evidence provided by the applicants as mentioned above, which shows that ORC can have pharmacological activity in haemostasis. In keeping with my conclusions as regards the SmPC, I can, however, find nothing in any of the above passages of the EPAR that suggest ORC is acting as anything other than a physical haemostat in the EVARREST medicinal product. For instance, sections 2.2.3. and 2.2.4. of the EPAR explicitly identify the active ingredients as thrombin and fibrinogen, and that ORC is an excipient. Section 2.1. states that "*oxidized regenerated cellulose is widely used during surgery as a topical absorbable haemostat*" (i.e. a physical haemostat), and also that "*the [polyglactin/ORC] matrix holds the fibrin clot at the site of bleeding and additionally offers a texture for blood components in order to support local haemostasis*". Providing support for haemostasis is not the same in my view as promoting haemostasis – I consider that the former is a passive or physical effect, the latter is an active or pharmacological effect

78 In addition to the points above highlighted by the examiner and the agent, in looking at the EPAR in its entirety, I am satisfied that the two biological components – human Fibrin and Human Thrombin – are the active substances in this medicinal product for the purposes of the SPC regulation. The ORC is part of the matrix that supports the substances which are responsible for the biological activity in terms of proving a

physical barrier to cover the area that is bleeding and presenting the biological substances in a manner that they can promote clot formation. As was noted in the basic patent, it is necessary to keep the ORC separate from the fibrinogen and the thrombin to avoid deactivation of the biological substances. This is summed up in my view in the discussion on the quality aspects of the medicinal product - see Section 2.2.1 (page 7) of the EPAR entitled 'introduction' to the Quality aspects of the medicinal product, it is stated that:

> "*The drug substances (Human Fibrinogen and Human Thrombin) are identical to those used in the currently approved product, EVICEL Solutions for Sealant (licence numbers EU/1/08/473/001, EU/1/08/473/002 and EU/1/08/473/003) manufactured by OMRIX Biopharmaceuticals NV.*
>
> *EVARREST Fibrin Pad is a sterile bio-absorbable haemostatic combination product (ATC code: B02BC30) consisting of a flexible matrix coated with two biological components (Human Fibrinogen and Human Thrombin).*
>
> *The term "Sealant Matrix" is used to describe the pharmaceutical form of EVARREST. The strengths of the active substances on the Fibrin Pad are 8.1 mg/cm2 Human Fibrinogen and 40 IU/cm2 Human Thrombin. Each EVARREST unit is packaged in a Single Dose Container consisting of a polyester tray and lid assembly enclosed in a foil pouch. Package size is one 10.2 cm x 10.2 cm Fibrin Pad.*
>
> *The mechanism of action follows the principles of normal physiological fibrin clot formation. Upon contact with a bleeding wound surface, the biological components (Human Fibrinogen and Human Thrombin) on the composite matrix hydrate and the subsequent fibrinogen – thrombin reactions initiate the last step of blood clot formation.*
>
> *The manufacture of Fibrin Pad comprises three distinct production processes: 1) manufacture of the composite matrix, 2) manufacture of the active biological ingredients (Human Fibrinogen and Human Thrombin drug substances) and 3) manufacture of the finished combination product*."

79 The discission under Section 2.3.3. on the Pharmacokinetics summarises the studies:

> *"focussing on the haemostatic properties of Fibrin Pad, on the basis of the physical effect of a matrix pad and active clotting proteins, fibrinogen and thrombin, included a non-traditional ADME absorption study (see table 2 below).".*

80 The applicant brought my attention to the clinical study identified as study 400-07—002 who used similar sized pads of the oxidised regenerated cellulose product SURGICEL [27] as control when compared to the same size pad of EVARREST. The difference between SURGICEL and EVARREST is that the latter also includes the biological substances fibrinogen and thrombin. In my view the results of this trial show that the better outcomes with EVARREST is down to the presence of the biological components. Although, there may be a small contribution to the haemostatic effect exerted by the EVARREST from the ORC, most of this is clearly resulting from the presence of the thrombin and the fibrin. In referring to some of the additional material provided by the applicant, at the hearing, the agent argued that the haemostatic effect

[27] *SURGICEL is a registered trademark (RTM) in the UK*

of the ORC component of EVARREST is significant and that it is not just of a passive or physical effect. The agent in effect directed me to consider that the additional evidence shows that SURGICEL which itself is a form of ORC has a pharmacological effect, i.e. it causes active haemostasis and as such the ORC in EVARREST can be considered to be behaving in the same way. However, I do not consider that this argument is sufficient to support a conclusion that ORC is acting as an active ingredient in combination with Fibrin and Thrombin. The study conducted using SURGICEL as control, shows that there is significantly better results from EVARREST in terms of achieving haemostasis when compared to the SURGICEL , i.e., the components of the medicinal product that are exerting the therapeutic action of interest are the fibrin and the thrombin and that this is more efficient than using SURGICEL alone. I do not consider that I can read anymore into the presence of ORC in EVARREST other than its main purpose as part of the EVARREST product is to provide a physical barrier to cover the bleeding wound area and bring the biologically active component into close proximity to the blood and then to produce a form of product that can be broken down by the body once its therapeutic activity has been achieved.

81 Having concluded that both the EPAR, and the SmPC (which was already mentioned above and which forms part of the marketing authorisation), make it clear that ORC is an excipient and not an active ingredient, it is therefore not appropriate for me to go on to consider whether the references within the EPAR (and SmPC) to ORC being "a haemostat" might relate to a haemostat that has a pharmacological effect, because both of these documents indicate that ORC has a physical effect only. I should also add that the reference in the Introduction of the EPAR[28] to '*two haemostatically active components*', in my opinion, does not mean 'active' as in pharmacologically active: it merely means that both of these components (i.e. the flexible matrix of polyglactin/ORC and the coating of two biological components (fibrinogen/thrombin) both contribute to haemostasis. The final sentence of this paragraph makes clear that the matrix "*holds the fibrin clot at the site of bleeding and additionally offers a texture for blood components in order to support local haemostasis*".

82 At the hearing, Mr Holland emphasised the need for caution in overly analysing different subsections of documents such as the SmPC and EPAR, which are not primarily created for the purposes of the SPC Regulation, in identifying what the active ingredients are. However, while I accept his point in this regard in so far as it goes, I consider that both examiner and agent need to take account of the SmPC and EPAR as a whole and not just focus on the specific parts that offer most for their respective arguments. In this manner, the SmPC and the EPAR provide detail on what therapeutical activity has been investigated and what contributions the different parts of the medicinal product make to its activity.

83 Having taken into account the arguments from the applicant further expanded at the hearing, I am of the view that both the SmPC and the EPAR are clear in referring to ORC as an excipient that acts as a physical haemostat only. The lack of any suggestion of a pharmacological effect cannot be ignored.

84 The SmPC and the EPAR describe the work that has been done to establish that the medicinal product provides an effective therapy. In this case, ORC was not assessed

[28] *see final paragraph of Section 2.1 Introduction in the EPAR*

as a part of the medicinal product that contributed directly to the pharmacological action but as an additional element of that product that helps achieve the pharmacological action – in this case providing a support for the clotting of blood in wounds covered by the medicinal product. While, it may well be possible that such an additional element may have other useful properties that can be explained by reference to materials other than the SmPC and the EPAR, that is in effect coincidental. However, this additional element is not key to establishing the effectiveness of the medicinal product in the achieving the therapeutic activity described in the marketing authorisation and its related SmPC and EPAR. It is the work carried out to establish the effectiveness of the medicinal product in achieving the therapeutic activity that results in the delay to the exploitation of the patent, that the SPC system is in place to compensate for (as set down in the recitals to the SPC Regulation). On balance, I do not think that it would be consistent with the purpose of the SPC system, if it was possible to obtain SPC protection for a medicinal product comprising active ingredients which have previously been the subject of a SPC because they have been able to provide some further evidence to show that another element of the medicinal product may share some of the same properties as the active ingredients even though this has not been investigated as part of the work to obtain the marketing authorisation and is not the main reason why this additional element in the medicinal product is included.

Conclusion

85 Taking all of the above into account, I consider the SmPC, and the EPAR for authorised medicinal product EVARREST, refer to ORC as a physical haemostat only, and are silent as to any pharmacological effect that means that ORC can be considered as an active ingredient in a similar manner to thrombin and fibrin.

86 In the absence of any pharmacological effect, and given my interpretation of *the relevant case law*, I do not consider that ORC can be deemed as an active ingredient within the meaning of Article 1(b) of the Regulation. Since it cannot be considered an active ingredient, the only active ingredients in EVARREST are thrombin and fibrinogen. However, as has already been noted above, and as was acknowledged by the applicants, the combination of these two active ingredients has already been the subject of two previous marketing authorisations.

87 As a consequence, application SPC/GB14/029 cannot be considered as an application for a combination of three active ingredients, i.e., thrombin, fibrinogen and oxidised regenerated cellulose, but rather it is an application for a combination of two active ingredients (thrombin, fibrinogen). As such, this application does not meet the requirement of Article 3(d) of Regulation 469/2009 and is rejected under Article 10(2) of this regulation.

Other Matters

Impact of withdrawn marketing authorisation for EVARREST

88 As is clear from Section 97, Section 128B and section 3(2) of Schedule 4A to the Patents Act 1977, the applicant, given my conclusion above, has a right to appeal this decision should they so choose. Deciding to do so is of course entirely a matter for the applicant in the present case.

89 If, in the circumstances of an appeal, my conclusion in relation to Article 3(d) was found to be in error, it would be necessary, in my view, to then take account of the fact that, at present, there is no marketing authorisation in force in the UK for the medicinal product EVARREST.

90 Under the Medicines Directive[10] and the EMA Regulation[3], a central marketing authorisation such as that cited in support of the present application when granted is valid for an initial period of five years[21]. It can be renewed after five years, subject to a positive re-evaluation of the risk-benefit balance by the relevant competent authority (in this case the EMA). In usual circumstances, the MA, if renewed, shall be valid for an unlimited period unless the medicinal product for which it provides authorisation is not actually placed on the market in the respective territory for a period of three consecutive years[29]. As I have already noted above, the marketing authorisation in the present case was withdrawn "for commercial reasons" within this first five-year period and so was not subject to the renewal process and re-evaluation of the risk-benefit balance.

91 At the hearing, the agent acknowledged that if there is no MA in force, then the SPC which relies on it cannot enter into force upon payment of the relevant fees, when the basic patent that the SPC relies on, expires. I am satisfied that, as the MA was in force at the time that the application for the SPC at issue in this case was made, under Art 10(1), if the application meets the requirements of the regulation, then it has to be granted. There is no discretion in the term "shall" in Article 10(1). However, it is also the case that for a granted SPC what has not yet come into force, if the MA is withdrawn, as is the case here and as is referred to Article 14(d) of the regulation, the SPC shall lapse. There is similarly no discretion in the term "shall" in Article 14

92 If my conclusion in relation to Article 3(d) above is in error, and it was found, on appeal, that this SPC application does meet the requirements of Article 3 and should be granted, it would be necessary to consider the issue of whether or not the SPC can enter into force. It is not possible for an SPC for an active ingredient (or combination of active ingredients) to enter into force upon expiry of the basic patent without a valid marketing authorisation also being in force to place the medicinal product comprising that active ingredient (or combination of active ingredients) on the market in the UK.

93 I wrote to the applicant prior to the hearing asking to be addressed on this point in addition to a number of other points. At the hearing, the agent accepted that if the situation does not change from that at present, there would be no SPC in the future. It would in effect lapse because there is (currently) no marketing authorisation in force in the UK for EVARREST. The agent indicated that sales of this medicinal product in US are continuing and showing growth and, given the reason for its withdrawal, if

[29] See Article 24 of Directive 2001/83 and Article 14 of the EMA Regulation

conditions for this sort of product improved in Europe, re-launch would be explored by the applicant.

Appeal

94 Any appeal must be lodged within 28 days after the date of this decision.

Dr L CULLEN
Deputy Director, acting for the Comptroller