Neutral Citation Number: [2017] EWHC 14 (Pat)

Case No: CH/2016/000229

**IN THE HIGH COURT OF JUSTICE**
**CHANCERY DIVISION**
**PATENTS COURT**

Rolls Building
Fetter Lane, London EC4A 1NL

Date: 13 January 2017

**Before** :

**MR JUSTICE ARNOLD**

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**Between :**

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| **ABRAXIS BIOSCIENCE LLC** | **Appellant** |
| **- and -** | |
| **THE COMPTROLLER-GENERAL OF PATENTS** | **Respondent** |

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**Richard Meade QC** and **William Duncan** (instructed by **Carpmaels & Ransford LLP**) for the **Appellant**
**Brian Nicholson** (instructed by the **Treasury Solicitor**) for the **Respondent**

Hearing dates: 20-21 December 2016

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# Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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MR JUSTICE ARNOLD

**MR JUSTICE ARNOLD :**

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## Introduction

1. This is an appeal by the Appellant ("Abraxis") against the decision of Dr Jim Houlihan, Deputy Director, acting for the Comptroller-General of Patents, dated 26 August 2016 (O/410/16) to refuse Abraxis' SPC Application No. GB/09/046 for a product described as "paclitaxel formulated as albumin bound nanoparticles" ("the Application") on the ground that it did not comply with Article 3(d) of European Parliament and Council Regulation 469/2009/EC of 6 May 2009 concerning the supplementary protection certificate for medicinal products (codified version) ("the SPC Regulation"). Abraxis calls the product paclitaxel formulated as albumin bound nanoparticles "nab-paclitaxel". For convenience I shall adopt that terminology, but I must make it clear that in doing so I am not intending to pre-judge the issues arising on this appeal. The importance of this point will become clear below.

2. Abraxis markets nab-paclitaxel under the trade mark Abraxane pursuant to marketing authorisation EU/1/07/428/001 ("the Abraxane MA"). The product is indicated for the treatment of metastatic breast cancer, metastatic adenocarcinoma of the pancreas and non-small cell lung cancer, used alone or together with other anti-cancer treatments. Prior to the date of the Abraxane MA, paclitaxel had been marketed by other parties under the trade marks Paxene and Taxol pursuant to earlier marketing authorisations. The details of the earlier marketing authorisations are immaterial for present purposes. Nab-paclitaxel is protected by European Patent (UK) No. 0 961 612 ("the Patent").

3. Abraxis contends that the active ingredient of the medicinal product authorised by the Abraxane MA is not paclitaxel, but nab-paclitaxel. It is common ground that, if this is correct, the Abraxane MA is the first marketing authorisation for nab-paclitaxel and that the Application complies with Article 3(d) of the SPC Regulation. The hearing officer held, however, that the active ingredient of the medicinal product authorised by the Abraxane MA is paclitaxel. It is common ground that the Abraxane MA is not the first marketing authorisation for paclitaxel. Accordingly, the hearing officer held that the Application did not comply with Article 3(d).

4. In the alternative, Abraxis contends that nab-paclitaxel is a new and inventive formulation of an old active ingredient, namely paclitaxel, and that Article 3(d) should be interpreted as permitting the grant of an SPC for a product which consists of a new and inventive formulation of an old active ingredient. The hearing officer held, however, that, although Article 3(d) permitted the grant of an SPC for a new and inventive *therapeutic use* of an old active ingredient, it did not permit the grant of an SPC for a new and inventive *formulation* of an old active ingredient.

5. Abraxis' contentions raise questions to the proper interpretation of Articles 1(b) and 3(d) of the SPC Regulation. Abraxis submits that the answers to the questions are not clear, and therefore the questions should be referred to the Court of Justice of the European Union. In support of this submission, Abraxis relies on the fact that SPCs have been granted for nab-paclitaxel in nine EU Member States (Austria, Denmark, Finland, France, Greece, Italy, Luxembourg, Portugal and Spain), refused in two Member States (Sweden and the UK) and are the subject of pending applications in a further three Member States (Germany, the Netherlands and Ireland) and also in Switzerland. The Respondent ("the Comptroller") submits that the answers to the questions are clear, and accordingly no reference is necessary.

The Patent

6. The Patent is entitled "Protein stabilized pharmacologically active agents and their use". It is not necessary for present purposes to describe the Patent in any detail. It is sufficient to set out claims 1, 32 and 33, which are in the following terms:

> "1. A composition comprising particles of a solid or liquid, substantially water insoluble pharmacologically active agent, coated with protein, wherein the average diameter of said particles is less than 200 nm, wherein said protein coating has free protein associated therewith, and wherein a portion of said pharmacologically active agent is contained within said protein coating and a portion of said pharmacologically active agent is associated with said free protein.
>
> 32. A composition according to any one of claims 1 to 22 for use in eliminating cancer cells, wherein said composition is cremaphor free and said pharmacologically active agent is an antineoplastic.
>
> 33. A composition according to claim 32, wherein said antineoplastic is paclitaxel and said protein is albumin."

7. It can be seen from this that claim 33 covers a composition comprising particles of a pharmacologically active agent, namely paclitaxel, coated with a protein, namely, albumin, in which the average diameter of the particles is less than 200 nm and part of the paclitaxel is contained within the albumin coating and part is associated with free albumin associated with the coating.

Nab-paclitaxel

8. The hearing officer made the following findings about nab-paclitaxel. Nab-paclitaxel comprises nanoparticles of paclitaxel coated with albumin. This coating has further free albumin associated with it. Some paclitaxel is contained within the albumin coating, and some is associated with the free albumin. Albumin and paclitaxel are tightly bound together in the particles, and this interaction is stronger than that between free albumin and paclitaxel, but it does not consist of a covalent bond. (Although the hearing officer was not explicit as to the nature of the interaction, my understanding is that it is a hydrophobic interaction.) The binding is sufficiently tight that the albumin and paclitaxel are transported across the cell membrane as a single unit.

9. The hearing officer concluded at [154] that nab-paclitaxel consists of an active ingredient, namely paclitaxel, together with a carrier, namely albumin, which "enables paclitaxel to be effective in exerting its own cytotoxic effects on tumours".

10. Nab-paclitaxel behaves materially differently to paclitaxel in a number of ways which the hearing officer summarised at [183] as follows:

> "(i) nab-paclitaxel displays more effectiveness than paclitaxel in treating some tumours either alone or in combination with other anti-cancer agents; (ii) … nab-paclitaxel offers advantages over conventional cremaphor-based formulations of paclitaxel in terms of patient tolerability; (iii) … nab-paclitaxel depletes the tumour microenvironment and kills cells other than cancer cells within it; (iv) … nab-paclitaxel is better than paclitaxel in killing tumour cells *in vitro;* (v) … nab-paclitaxel is transported particularly effectively to tumour locations and … (vi) nab-paclitaxel remains intact inside the cell."

Abraxane

11. There is no dispute that Abraxane required prolonged and expensive research to develop, with the consequence that it took a significant period of time for Abraxis to obtain the Abraxane MA following the filing of the application for the Patent.

The SPC Regulation

12. The SPC Regulation enables the proprietor of a patent for a medicinal product to obtain an SPC which extends the duration of the patent with respect to that product so as to compensate the proprietor for the effective loss of patent term caused by the need to obtain a marketing authorisation before the product can be marketed.

13. The SPC Regulation includes the following recitals:

"[3] Medicinal products, especially those that are the result of long, costly research will not continue to be developed in the Community and in Europe unless they are covered by favourable rules that provide for sufficient protection to encourage such research.

[4] At the moment the period that elapses between the filing of an application for a patent for a new medicinal product and authorisation to place the medicinal product on the market makes the period of effective protection under the patent insufficient to cover the investment put into the research.

[5] This situation leads to a lack of protection which penalises pharmaceutical research.

[6] There exists a risk of research centres situated in the Member States relocating to countries that offer greater protection.

[7] A uniform solution at Community level should be provided for, thereby preventing the heterogeneous development of national laws leading to further disparities which would be likely to create obstacles to the free movement of medicinal products within the Community and thus directly affect the establishment and the functioning of the internal market.

[8] Therefore, the creation of a supplementary protection certificate granted, under the same conditions, by each of the Member States at the request of the holder of a national or European patent relating to a medicinal product for which marketing authorisation has been granted is necessary. A Regulation is therefore the most appropriate legal instrument."

14. Articles 1, 3 and 8 of the SPC Regulation provide, so far as relevant:

"*Article 1*

**Definitions**

For the purpose of this Regulation:

(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) 'basic patent' means a patent which protects a product as defined in (b) as such, a process to obtain a product or an application of a product, and which is designated by its holder for the purpose of the procedure for grant of a certificate;

…

*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 -

…

(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 Directive 2001/82/EC, as appropriate;

…

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

*Article 8*

**Content of the application for a certificate**

1. The application for a certificate shall contain:

…

(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 Article 14 of Directive 2001/82/EC;

…"

Interpretation of the SPC Regulation

15. As is common ground, it is well established that the correct approach to the interpretation of the SPC Regulation is that stated by the CJEU in Case C-482/07 *AHP Manufacturing v Bureau voor de Industriele Eigendom* [2009] ECR I-7295 at [27]:

> "Next, the Court observes that the second sentence of Article 3(2) of Regulation No 1610/96 must be interpreted not solely on the basis of its wording, but also in the light of the overall scheme and objectives of the system of which it is a part (see,

> by analogy, Case C-292/00 *Davidoff* [2003] ECR I-389, paragraph 24)."

16. As is also common ground, the SPC Regulation pursues a number of different objectives and aims to strike a balance between them. This was well described by Advocate General Trstenjak in her opinion in Case C-130/11 *Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents* [EU:C:2012:268], [2013] RPC 23:

> "41. Those rules are intended to achieve a balance between the various interests at stake in the pharmaceutical sector. Those interests include, on the one hand, the interests of the undertakings and institutions, some of which pursue very cost-intensive research in the pharmaceutical sector and therefore favour an extension of the term of protection for their inventions in order to be able to balance out the investment costs. On the other hand, there are the interests of the producers of generic medicines who, as a consequence of the extension of the term of protection of the active ingredients under patent protection, are precluded from producing and marketing generic medicines. It is also relevant in this connection that, in general, the marketing of generic medicinal products has the effect of lowering the prices of the relevant medicinal products. Against that background, the interests of patients lie between the interests of the undertakings and institutions conducting research and those of the producers of generic medicines. That is because patients have an interest, on the one hand, in the development of new active ingredients for medicinal products, but, on the other, they also have an interest in those products then being offered for sale as cheaply as possible. The same applies to State health systems in general which, in addition, have a particular interest in preventing old active ingredients from being brought onto the market in slightly modified form under the protection of certificates but without genuine innovation and thereby artificially driving up expenditure in the health section.
>
> 42. Against the background of that complex situation as regards interests, Regulation 1768/92 sought to achieve a balanced solution taking due account of the interests of all parties. In view of the complexity of that balance of interests, it is necessary to proceed with great caution when making a teleological interpretation of the individual provisions of the regulation."

Interpretation of Articles 1(b) and 3(d): the problems

17. The interpretation of Articles 1(b) and 3(d) of the SPC Regulation (and its predecessor, Council Regulation 1768/92/EEC) has caused considerable difficulty over the years, as is illustrated by the successive judgments of the CJEU discussed below. It may be helpful if I attempt to explain the problems before turning to

consider the case law. Although the problems are in principle separate, they interact with each other.

18. The first problem is that the SPC Regulation contains no definition of the expression "active ingredient". How, therefore, does one decide what constitutes an "active ingredient" within the meaning of Article 1(b)? In particular, what is the position regarding (i) substances which, in one way or another, assist an active ingredient to achieve a particular therapeutic effect and (ii) combinations of such substances and that active ingredient? Some light is shed on this question by paragraphs 11 and 12 of the Commission's Explanatory Memorandum proposing what became Council Regulation 1768/92/EEC, which state (emphases added):

> "11. The proposal for a Regulation therefore concerns only new medicinal products. It does not involve granting a certificate for all medicinal products that are authorized to be placed on the market. Only one certificate may be granted for any one product, a product being understood to mean an active substance *in the strict sense*. Minor changes to the medicinal product such as a new dose, the use of a different salt or ester *or a different pharmaceutical form* will not lead to the issue of a new certificate.
>
> 12. However, the proposal is not confined to new products only. A new process for obtaining the product or *a new application of the product* may also be protected by a certificate. All research, whatever the strategy or final result, must be given sufficient protection."

19. The second problem is that Article 3(d) requires that the marketing authorisation relied upon be the first authorisation "to place the product on the market as a medicinal product". How is this requirement to be interpreted in circumstances where the same active ingredient or combination of active ingredients (depending, of course, on what is meant by "active ingredient") has previously been the subject of a marketing authorisation, but the new marketing authorisation is for a different formulation or a different therapeutic use of that active ingredient or combination of active ingredients?

Case law of the CJEU on Articles 1(b) and 3(d)

*Pharmacia*

20. In Case C-31/03 *Pharmacia Italia SpA* [2004] ECR I-10001 an SPC application had been made in Germany for the active ingredient cabergoline, which was protected by a basic patent filed in 1981. The application was based on a marketing authorisation for cabergoline granted for the human medicinal product Dostinex in Germany in June 1994. By virtue of the transitional provision contained in Article 19(1) of Regulation 1768/92/EEC, an SPC could only be granted for a product if, on the date that Regulation entered into force, it was protected by a basic patent and "the first authorization to place it on the market as a medicinal product in the Community was obtained after" 1 January 1988. The first authorisation for Dostinex in the Community had been granted in the Netherlands in October 1992, but there had been an earlier

authorisation for cabergoline as the active ingredient of a veterinary medicinal product called Galastop granted in Italy in January 1987. In these circumstances the Bundesgerichtshof (German Federal Court of Justice) referred the following question to the Court of Justice:

> "Is the grant of a supplementary protection certificate in a Member State of the Community on the basis of a medicinal product for human beings authorised in that Member State precluded by an authorisation to place the same product on the market as a veterinary medicinal product granted in another Member State of the Community before the date specified in Article 19(1) of the Protection Certificate Regulation, or is the sole determining factor the date on which the product was authorised in the Community as a medicinal product for human beings?"

21. The applicant argued that it was the date of first authorisation to place the product on the market for human use which was relevant, whereas the Commission and the United Kingdom contended that the relevant date was that of the first authorisation to place the product on the market for either human or veterinary use. Advocate General Jacobs advised the Court of Justice to adopt the latter interpretation. In his Opinion he considered Article 3(d) as well as Article 19(1), saying (footnote omitted):

> "49. In my view … the scheme of the Regulation … supports the view that the system of supplementary protection certificates which it establishes does not distinguish between medicinal products for, on the one hand, human use and, on the other hand, veterinary use, whether generally or for the specific purpose of Article 19.
>
> 50. In particular, the interpretation which I am suggesting appears consistent with Article 3(c) and (d). Article 3(c) includes as a condition for obtaining a certificate that the product has not already been the subject of a certificate and thus precludes the grant of more than one certificate for a product in a Member State even if it has been authorised as a medicinal product more than once. Article 3(d) includes a further condition that the marketing authorisation covering the product in respect of which a certificate is sought is the first authorisation to place that product on the market as a medicinal product and thus precludes the grant of a certificate on the basis of a second marketing authorisation even if an application for a certificate has not been made on the basis of the first marketing authorisation. Those provisions highlight the significance for the system put in place by the Regulation of the notion of one certificate per product without distinction depending on the number of authorisations. Although the authorisation referred to in Article 3(b) and (d) is the first authorisation in the Member State in which the application for the certificate is made whereas that at issue in Article 19 and the question referred is the first Community authorisation, to my mind the

> principle underlying Article 3 equally suggests that no distinction should be drawn for the purpose of Article 19 depending on whether the relevant authorisation was for human or veterinary use."

22. In its judgment the Court of Justice followed the Advocate General's advice, holding:

> "20. It follows, first, that the decisive factor for the grant of the certificate is not the intended use of the medicinal product and, second, that the purpose of the protection conferred by the certificate relates to any use of the product as a medicinal product without any distinction between use of the product as a medicinal product for human use and as a veterinary medicinal product.
>
> 21. Whilst noting that the term 'first marketing authorisation in the Community' must be interpreted in the same way in each of the provisions of the regulation in which it is used, it should be pointed out that, according to the sixth recital in its preamble, that regulation seeks to provide a uniform solution at Community level to the problem of inadequate patent protection, thereby preventing the heterogeneous development of national laws leading to further disparities which would be likely to create obstacles to the free movement of medicinal products within the Community. However, an interpretation such as that proposed by Pharmacia would prevent the realisation of that objective. Under Pharmacia's interpretation, the duration of the protection conferred by the certificate, calculated in accordance with Article 13 of the regulation, might be different for the same product.
>
> 22. Lastly, and for the reasons set out in points 41 to 43 and 48 to 50 of the Advocate General's Opinion, it must be found that neither the purpose of Article 19 nor the broad logic of the regulation militate in favour of the interpretation put forward by Pharmacia."

*MIT*

23. In Case C-431/04 *Massachusetts Institute of Technology* [2006] ECR I-4089 the applicant had applied in Germany for an SPC for the product carmustine, either in combination with a polymeric biodegradable matrix called polifeprosan or alternatively on its own. The applicant relied on a marketing authorisation for the medicinal product Gliadel, which was used for the treatment of human brain tumours. Gliadel comprised carmustine as its active ingredient and polifeprosan as an excipient. Carmustine was a highly cytotoxic substance which was already covered by an earlier marketing authorisation for the treatment of brain tumours with inert excipients. Polifeprosan was a new excipient that enabled the slow release of carmustine from a disc implanted in the cranium after surgical removal of the tumor, thereby permitting the delivery of a higher but constant dose of carmustine. Accordingly to the applicant, the combined use of carmustine and polifeprosan extended the life expectancy of

patients by several months. Polifeprosan was the subject of a patent which the applicant relied on as the basic patent for the application.

24. The application was refused by the Deutsches Patent- und Markenamt (German Patent and Trade Mark Office) on the basis that (i) no SPC could be granted for the combination of carmustine and polifeprosan since that was not a combination of active ingredients within the meaning of Article 1(b); and (ii) no SPC could be granted for carmustine on its own since the marketing authorisation relied on was not the first authorisation to market carmustine contrary to Article 3(d). As I understand it, the applicant appealed against holding (i), but not holding (ii). In those circumstances the Bundesgerichtshof referred the following questions to the Court of Justice:

> "1. Does the concept of 'combination of active ingredients of a medicinal product' within the meaning of Article 1(b) of Regulation [1768/92/EEC] mean that the components of the combination must all be active ingredients with a therapeutic effect?
>
> 2. Is there a 'combination of active ingredients of a medicinal product' also where a combination of substances comprises two components of which one component is a known substance with a therapeutic effect for a specific indication and the other component renders possible a pharmaceutical form of the medicinal product that brings about a changed efficacy of the medicinal product for this indication (*in vivo* implantation with controlled release of the active ingredient to avoid toxic effects)?"

25. Advocate General Léger advised the Court of Justice to rule that Article 1(b) should be interpreted as including a combination of an active ingredient (such as carmustine) with an excipient which is necessary for the therapeutic efficacy of the active ingredient (such as polifeprosan). He did so on the basis of the kind of teleological approach to interpretation contended for by Abraxis in the present case, saying that this was just the kind of costly innovation that the Regulation was designed to protect.

26. The Court of Justice did not follow the Advocate General's advice. Instead, it held as follows:

> "17. In the absence of any definition of the concept of 'active ingredient' in Regulation No 1768/92, the meaning and scope of those terms must be determined by considering the general context in which they are used and their usual meaning in everyday language (see, inter alia, Case 349/85 *Denmark* v *Commission* [1988] ECR 169, paragraph 9, and Case C-164/98 P *DIR International Film and Others* v *Commission* [2000] ECR I-447, paragraph 26).
>
> 18. In this case, it is important to note that it is common ground, as the file in this case shows, that the expression 'active ingredient' is generally accepted in pharmacology not to

include substances forming part of a medicinal product which do not have an effect of their own on the human or animal body.

19. In that regard, attention must be drawn to the fact that in point 11 of the Explanatory Memorandum to the Proposal for a Council Regulation (EEC), of 11 April 1990, concerning the creation of a supplementary protection certificate for medicinal products (COM(90) 101 final), to which the French Government referred in its oral observations, it is specified that '[t]he proposal for a Regulation therefore concerns only new medicinal products. It does not involve granting a [SPC] for all medicinal products that are authorised to be placed on the market. Only one [SPC] may be granted for any one product, a product being understood to mean an active substance in the strict sense. Minor changes to the medicinal product such as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the issue of a new [SPC].'

20. Therefore, the definition of 'product' in Article 1(b) of Regulation No 1768/92 does not in any way conflict with that referred to by the Commission in point 11 of that explanatory memorandum.

21. In fact, it is apparent from that memorandum that the pharmaceutical form of the medicinal product, to which an excipient may contribute, as noted by the Advocate General in point 11 of his Opinion and the French Government at the hearing, does not form part of the definition of 'product', which is understood to mean an 'active substance' or 'active ingredient' in the strict sense.

…

25. In the light of the foregoing, the inevitable conclusion is that a substance which does not have any therapeutic effect of its own and which is used to obtain a certain pharmaceutical form of the medicinal product is not covered by the concept of 'active ingredient', which in turn is used to define the term 'product'.

26. Therefore, the alliance of such a substance with a substance which does have therapeutic effects of its own cannot give rise to a 'combination of active ingredients' within the meaning of Article 1(b) of Regulation No 1768/92.

27. The fact that the substance without any therapeutic effect of its own renders possible a pharmaceutical form of the medicinal product necessary for the therapeutic efficacy of the substance which does have therapeutic effects cannot invalidate that interpretation.

> 28. As shown by paragraphs 6 and 7 of this judgment, carmustine is an active ingredient which must be combined with other substances, in particular inert excipients, to be therapeutically effective. More generally, as observed by the Advocate General in point 11 of his Opinion and by the French and Netherlands Governments, it is apparently not unusual for substances which render possible a certain pharmaceutical form of the medicinal product to influence the therapeutic efficacy of the active ingredient contained in it.
>
> 29. Thus, a definition of 'combination of active ingredients of a medicinal product' which includes a combination of two substances, only one of which has therapeutic effects of its own for a specific indication, the other rendering possible a pharmaceutical form of the medicinal product which is necessary for the therapeutic efficacy of the first substance for that indication, might, on any view, create legal uncertainty in the application of Regulation No 1768/92, as the French Government pointed out at the hearing. Whether a substance without any therapeutic effect of its own is necessary for the therapeutic efficacy of the active ingredient cannot, in this case, be regarded as a sufficiently precise test.
>
> 30. Moreover, such a definition is liable to prevent the attainment of the objective referred to in the sixth recital in the preamble to Regulation No 1768/92, in the words of which a uniform solution at Community level should be provided for, thereby preventing the heterogeneous development of national laws leading to further disparities which would be likely to create obstacles to the free movement of medicinal products within the Community and thus directly affect the establishment and the functioning of the internal market.
>
> 31. In those circumstances, the answer to the questions referred must be that Article 1(b) of Regulation No 1768/92 must be interpreted so as not to include in the concept of 'combination of active ingredients of a medicinal product' a combination of two substances, only one of which has therapeutic effects of its own for a specific indication, the other rendering possible a pharmaceutical form of the medicinal product which is necessary for the therapeutic efficacy of the first substance for that indication."

27. Although the Court did not refer to its earlier judgment in *Pharmacia*, and *Pharmacia* did not dictate the decision in *MIT*, the Court's decision in *MIT* was consistent with the earlier decision.

*Yissum*

28. In Case C-202/05 *Yissum Research and Development Company of the Hebrew University of Jerusalem v Comptroller-General of Patents* [2007] ECR I-2839 the

applicant applied for an SPC for the product calcitriol either alone or in combination with an ointment base. The applicant relied upon (i) a second medical use patent, the claims of which were directed to the use of calcitriol in topical treatment of skin disorders including psoriasis, and (ii) a marketing authorisation for Silkis ointment, which comprised calcitriol as the active ingredient with various carriers and was authorised for the topical treatment of psoriasis. The application was refused by the Comptroller because there were two earlier marketing authorisations for medicinal products containing calcitriol as the active ingredient, namely Calcijex and Rocaltrol. Calcijex was authorised for the management of hypocalcaemia in patients undergoing dialysis for chronic renal failure. Rocaltrol was authorised for administration to patients with chronic renal failure or post-menopausal osteoporosis.

29. On the applicant's appeal, I referred three questions to the Court of Justice ([2004] EWHC 2880 (Pat)]). Two of those were subsequently withdrawn in the light of the Court's judgment in *MIT*. The remaining question was as follows:

> "In a case in which the basic patent protects a second medical application of a therapeutic agent, what is meant by 'product' in Article 1(b) of the Regulation and in particular does the application of the therapeutic agent play any part in the definition of 'product' for the purpose of the Regulation?"

30. The Court of Justice gave its answer to that question by reasoned order on the basis that the answer to it could be clearly deduced from the existing case law, and in particular *Pharmacia* and *MIT*. In its order the Court held:

> "17. It is clear from *Massachusetts Institute of Technology*, and, in particular, from paragraphs 19, 21, 23 and 24 of that judgment, that the concept of 'product' referred to in Article 1(b) of Regulation No 1768/92 must be interpreted strictly to mean 'active substance' or 'active ingredient'.
>
> 18. It follows that the concept of 'product' cannot include the therapeutic use of an active ingredient protected by a basic patent.
>
> 19. Moreover, the same interpretation can be inferred from paragraph 20 of the judgment in Case C-31/03 *Pharmacia Italia* [2004] ECR I-10001, in which the Court held that 'the decisive factor for the grant of the certificate is not the intended use of the medicinal product and … the purpose of the protection conferred by the certificate relates to any use of the product as a medicinal product without any distinction between use of the product as a medicinal product for human use and as a veterinary medicinal product'.
>
> 20. Consequently, the answer to the question referred must be that Article 1(b) of Regulation No 1768/92 is to be interpreted as meaning that in a case where a basic patent protects a second medical use of an active ingredient, that use does not form an integral part of the definition of the product."

31. It can be seen from this that the Court of Justice confirmed that the concept of "product" in Article 1(b) of the Regulation was to be interpreted strictly and could not include the therapeutic use of the active ingredient, or even whether the medicinal product was for human use or for veterinary use.

*Neurim*

32. In Case C-130/11 *Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents* [EU:C:2012:489], [2012] RPC 23 melatonin, a naturally occurring hormone, had been marketed by Hoechst under the trade mark Regulin for regulating the seasonal breeding activity of sheep pursuant to a patent applied for in 1987 and a marketing authorisation granted in 2001 ("the Regulin MA"). Neurim marketed melatonin under the trade mark Circadin for the treatment of insomnia in humans pursuant to a patent applied for in 1992 and a marketing authorisation granted in 2007 ("the Circadin MA"). Neurim applied for an SPC in respect of Circadin. The Comptroller-General refused the application on the ground that it did not comply with Article 3(d) of the SPC Regulation since the Circadin MA was not the first authorisation to place melatonin on the market, the Regulin MA was. I dismissed Neurim's appeal ([2010] RPC 22, [2010] RPC 22) having considered *Pharmacia*, *MIT* and *Yissum*, but the Court of Appeal referred five questions to the Court of Justice ([2011] EWCA Civ 228, [2011] RPC 19). Questions 1 and 3 were as follows:

> "1. In interpreting Art.3 of Regulation EEC No. 1768/92 [now Regulation (EC) No. 469/2009 ] ('the SPC Regulation'), when a marketing authorisation (A) has been granted for a medicinal product comprising an active ingredient, is Art.3(d) to be construed as precluding the grant of an SPC based on a later marketing authorisation (B) which is for a different medicinal product comprising the same active ingredient where the limits of the protection conferred by the basic patent do not extend to placing the product the subject of the earlier MA on the market within the meaning of Art.4 ?
>
> …
>
> 3. Are the answers to the above questions different if the earlier marketing authorisation has been granted for a veterinary medicinal product for a particular indication and the later marketing authorisation has been granted for a medicinal product for human use for a different indication?"

33. Counsel for Abraxis pointed out that, when giving the judgment of the Court of Appeal, Jacob LJ had expressed the opinion that Neurim was correct to contend that Article 3(d) should interpreted as meaning that the authorisation referred to in Article 3(b) was that first *relevant* authorisation, *i.e. the first authorisation within the scope of the basic patent*, to place the product on the market as a medicinal product, saying (emphasis added):

> "28. We consider that Neurim's arguments are not only tenable: in our view they are right. Many kinds of valuable pharmaceutical research will not get the encouragement or reward they deserve

> if they are not. Pharmaceutical research is not confined to looking for new active compounds. *New formulations of old active substances are often sought. Most are unpatentable but from time to time a real invention is made and patented.*
>
> 29. Moreover there is much endeavour to find new uses for known active ingredients. The European Patent Convention 2000 has indeed made the patenting of inventions in this area clearer. Its effect is that a patent for a known substance or composition for use in a method of treatment is not to be regarded as old (and hence unpatentable) unless use for that method is known. It would be most unfortunate if second medical use patents could not get the benefit of an SPC."

(As counsel for Abraxis also pointed out, in this respect Jacob LJ was echoing what he had previously said in *Generics (UK) Ltd v Daiichii Pharmaceuticals Co Ltd* [2009] EWCA Civ 646, [2009] RPC 23 at [79] citing his own earlier observations at first instance in *Draco's Application* [1996] RPC 417 at 439.)

34. In her Opinion Advocate General Trstenjak advised the Court of Justice to answer the first question as contended for by Neurim. Although she acknowledged that a literal interpretation of Article 3(d) meant that no SPC could be granted to Neurim since the Circadin MA was not the first authorisation to place the active ingredient of the product, melatonin, on the market (see [21]-[27]), she considered that a teleological interpretation of Article 3(d) led to a different conclusion (see [28]-[57]). It is a striking feature of the Advocate General's opinion that there is no mention whatsoever of the decisions in *Pharmacia*, *MIT* or *Yissum*. On the other hand, she did note that there were two lines of the Court's case law which were "difficult to reconcile": a first line, including cases such as *AHP* and Case C-322/10 *Medeva BV v Comptroller-General of Patents, Designs and Trade Marks* [2011] ECR I-12051, which favoured a broader interpretation of the conditions for the grant of an SPC, and a second line, including cases such as Case C-195/09 *Synthon BV v Merz Pharma GmbH & Co KGaA* [2011] ECR I-7011 and Case C-427/09 *Generics (UK) Ltd v Synaptech Inc* [2011] ECR I-7099, which favoured a stricter interpretation. As she made clear, her interpretation of Article 3(d) followed the first line (see [58]-[64]).

35. The Court of Justice essentially followed the Advocate General's advice. It considered the first and third questions together, which it interpreted at [18] as asking, in essence, "whether the provisions of Articles 3 and 4 of the SPC Regulation are to be interpreted as meaning that, in a case such as that in the main proceedings, the existence of an earlier MA for a veterinary medicinal product is sufficient to preclude the grant of an SPC for the product application which obtained the other MA". It answered that question as follows:

> "23. The reason given for the adoption of the SPC Regulation is the fact that the period of effective protection under the patent is insufficient to cover the investment put into pharmaceutical research and the regulation thus sought to make up for that insufficiency by creating an SPC for medicinal products (see *Medeva*, paragraph 31, and *Georgetown University and Others*, paragraph 25).

> 24. It is apparent from paragraph 29 of the explanatory memorandum to the proposal for a Council Regulation (EEC) of 11 April 1990, concerning the creation of a supplementary protection certificate for medicinal products (COM(90) 101 final), that, like a patent protecting a 'product' or a patent protecting a process by which a 'product' is obtained, a patent protecting a new application of a new or known product, such as that at issue in the main proceedings, may, in accordance with Article 2 of the SPC Regulation, enable an SPC to be granted and, in that case, in accordance with Article 5 of the regulation, the SPC confers the same rights as conferred by the basic patent as regards the new use of that product, within the limits laid down by Article 4 of that regulation (see, by analogy, *Medeva*, paragraph 32, and order of 25 November 2011 in Case C-630/10 *University of Queensland and CSL*, ECR I-0000, paragraph 38).
>
> 25. Therefore, if a patent protects a therapeutic application of a known active ingredient which has already been marketed as a medicinal product, for veterinary or human use, for other therapeutic indications, whether or not protected by an earlier patent, the placement on the market of a new medicinal product commercially exploiting the new therapeutic application of the same active ingredient, as protected by the new patent, may enable its proprietor to obtain an SPC, the scope of which, in any event, could cover, not the active ingredient, but only the new use of that product.
>
> 26. In such a situation, only the MA of the first medicinal product, comprising the product and authorised for a therapeutic use corresponding to that protected by the patent relied upon for the purposes of the application for the SPC, may be considered to be the first MA of 'that product' as a medicinal product exploiting that new use within the meaning of Article 3(d) of the SPC Regulation.
>
> 27. In the light of all the above considerations, the answer to the first and third questions is that Articles 3 and 4 of the SPC Regulation are to be interpreted as meaning that, in a case such as that in the main proceedings, the mere existence of an earlier MA obtained for a veterinary medicinal product does not preclude the grant of an SPC for a different application of the same product for which an MA has been granted, provided that the application is within the limits of the protection conferred by the basic patent relied upon for the purposes of the application for the SPC."

36. As I observed in *AstraZeneca AB v Comptroller-General of Patents, Trade Marks and Designs* [2012] EWHC 2840 (Pat), [2013] RPC 25 at [52]-[53], the Court's judgment in *Neurim* (although not the actual decision) is problematic for two reasons.

37. First, it appears that the Court was intending to depart from its decisions in *Pharmacia*, *MIT* and *Yissum*, and in particular the decisions in *Pharmacia* and *Yissum*. This is not clear, however, since it did not refer to those decisions. Thus one does not know if those decisions are to be regarded as having been overruled, or as qualified in some unspecified manner.

38. Secondly, it does not appear that the Court was intending to depart from its earlier judgments in *Synthon* and *Generics*, since it cited *Synthon* at [20]. It is not clear to me, however, how *Neurim* is to be reconciled with those decisions. The reasoning which the Court relied on in *Neurim*, namely that the research required to obtain a patent and marketing authorisation for a second medical use of an active ingredient justifies the grant of an SPC for the second medical use despite the fact that the same active ingredient has already been lawfully marketed as a medicinal product, seems to me to be equally applicable to *Generics* and *Synthon*, albeit that those cases did not concern Article 3(d). As noted above, Advocate General Trstenjak drew attention to this difficulty in her opinion, yet the Court proceeded as if there was no problem.

*GSK*

39. In Case C-210/13 *Glaxosmithkline Biologicals SA v Comptroller-General of Patents, Designs and Trade Marks* [EU:C:2013:762], [2014] RPC 17 GSK applied for a supplementary protection certificate for "an oil in water emulsion comprising squalene, DL-α-tocopherol and polysorbate 80", an adjuvant known as AS03 which was protected by European Patent (UK) No 0 868 918. GSK subsequently applied for a supplementary protection certificate for "an adjuvanted influenza vaccine comprising an influenza virus component which is an influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak or has the potential to be associated with a pandemic outbreak, wherein the adjuvant is an oil in water emulsion comprising squalene, DL-α-tocopherol and polysorbate 80", a vaccine comprising an antigen and AS03 which was protected by European Patent (UK) No 1 618 889. In both applications GSK relied upon a marketing authorisation for a pre-pandemic influenza vaccine against the H5N1 subtype of influenza A virus marketed by GSK under the trade mark Prepandrix. The Comptroller-General of Patents decided that neither application was allowable as it stood since AS03 was not an "active ingredient" of Prepandrix, although she was prepared to give GSK an opportunity to amend the applications. On GSK's appeal against this decision, I referred the following questions to the Court of Justice ([2013] EWHC 619 (Pat), [2013] RPC 26):

> "1. Is an adjuvant which has no therapeutic effect on its own, but which enhances the therapeutic effect of an antigen when combined with that antigen in a vaccine, an 'active ingredient' within the meaning of Article 1(b) of [the SPC Regulation]?
>
> 2. If the answer to question 1 is no, can the combination of such an adjuvant with an antigen nevertheless be regarded as a 'combination of active ingredients' within the meaning of Article 1(b) of [the SPC Regulation]?"

40. The Court of Justice answered these questions together by reasoned order on the basis that the answer to them could be clearly deduced from the existing case law, and in particular *MIT*.

41. In its order the Court began (at [27]-[34]) by recapitulating what it had said in *MIT* at [17]-[29]. It went on:

> "35. Those considerations also apply to a situation such as that in the main proceedings, in which an adjuvant is in issue which, as it has no therapeutic effects on its own, cannot be regarded as an 'active ingredient' within the meaning of Article 1(b) of Regulation No. 469/2009 .
>
> 36. That distinction between 'active ingredient' and 'adjuvant' is also made quite clear in s.3.2.2.1 of Part 1, entitled 'Standardised marketing authorisation dossier requirements', of Annex I to Directive 2001/83, as amended by Directive 2003/63. That annex lists the particulars and documents to be submitted in support of an MA application in accordance, inter alia, with Article 8(3) of that directive, as amended.
>
> 37. Section 3.2.2.1 states as follows:
>
> 'A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:
>
> – the active substance(s),
>
> – the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
>
> – the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.).
>
> …'
>
> 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."

42. Accordingly, the Court held that Article 1(b) "must be interpreted as meaning that, just as an adjuvant does not fall within the definition of 'active ingredient' within the

meaning of that provision, so a combination of two substances, namely an active ingredient having therapeutic effects on its own, and an adjuvant which, while enhancing those therapeutic effects, has no therapeutic effect on its own, does not fall within the definition of 'combination of active ingredients' within the meaning of that provision".

43. Importantly, the Court also said this:

> "43. With regard to the judgment in *Neurim Pharmaceuticals (1991)*, it should be noted that in that judgment, as suggested by the Court of Appeal (England and Wales) (Civil Division), the Commission and Advocate General Trstenjak in her Opinion in the case giving rise to that judgment, the Court held, inter alia, at 24 of the judgment, that, like a patent protecting a 'product' or a patent protecting a process by which a 'product' is obtained, a patent protecting a new application of a new or known product may now, in accordance with Article 2 of Regulation No. 469/2009, enable an SPC to be granted and, in that case, in accordance with Article 5 of that regulation, the SPC confers the same rights as conferred by the basic patent as regards the new use of that product, within the limits laid down by Article 4 of that regulation.
>
> 44. However, the Court did not, in that judgment, cast doubt on the principle that Article 1(b) of Regulation No. 469/2009 is to be interpreted narrowly, as held in the judgment in *Massachusetts Institute of Technology*, to the effect that the term 'product' cannot cover a substance which does not correspond to the definition of 'active ingredient' or that of 'combination of active ingredients'."

44. This makes it clear that the Court considers that there is no inconsistency between its decisions in *MIT* and *GSK* and its decision in *Neurim*. I have no difficulty in accepting that it is possible to reconcile *Neurim* with *MIT* and *GSK* in the way that the Court indicates: Article 1(b) must be strictly interpreted, while Article 3(d) may be more broadly interpreted. It is notable, however, that the Court did not say anything about the decisions in *Pharmacia* and *Yissum*, which are less easy to reconcile with *Neurim*. This seems to imply that *Pharmacia* and *Yissum* are no longer to be regarded as authoritative, or at least that they should only be regarded as authority with respect to the specific facts and questions considered in those cases. It would be more helpful to the national courts if the Court would expressly state when its earlier decisions are no longer to be regarded as authoritative, or as restricted to their own facts, rather than leaving the national courts to try to work this out for themselves.

*Forsgren*

45. In Case C-631/13 *Forsgren v Österreichisches Patentamt* [EU:C:2015:13] Mr Forsgren was the proprietor of a patent relating to Protein D, an IgD-binding protein of *Haemophilus influenzae*. Protein D was present in a pneumococcal vaccine for paediatric use marketed under the trade mark Synflorix. The marketing authorisation for Synflorix, and in particular the Summary of Product Characteristics

("SmPC"), described Synflorix as a vaccine composed of 10 pneumococcal polysaccharide serotypes which were conjugated to carrier proteins and adsorbed on to aluminium phosphate. In eight of those serotypes, Protein D was the carrier protein. The excipients of the vaccine were said to be sodium chloride and water for injection. The vaccine was indicated for immunisation against "invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children" of certain ages. The SmPC stated that there was "insufficient evidence that Synflorix provides protection against … non-typeable *Haemophilus influenza*".

46. Mr Forsgren applied to the Österreichisches Patentamt (Austrian Patent Office) for an SPC for Protein D. That application was refused on the ground that Protein D was just an excipient. The Board of Appeal of the Österreichisches Patentamt upheld that decision. The Board found that Protein D was not present as such in Synflorix, but was covalently bonded to other active ingredients. Mr Forsgren appealed to the Oberster Patent- und Markensenat (Austrian Supreme Patent and Trade Mark Adjudication Tribunal), which found that Protein D had two independent effects: (i) as a vaccine against a middle ear inflammation caused by non-typeable *Haemophilus influenzae* bacteria; and (ii) as an adjuvant to the substances effective against pneumococci (pneumococcal polysaccharides). It referred the following questions to the Court of Justice:

> "1. Under Article 1(b) and Article 3(a) and (b) of [the SPC Regulation], provided that the other conditions are met, may [an SPC] be granted for an active ingredient protected by a basic patent (in this case, Protein D) where that active ingredient is present in a medicinal product (in this case, Synflorix) as part of a covalent (molecular) bond with other active ingredients but none the less retains an effect of its own?
>
> 2. If Question 1 is answered in the affirmative:
>
> (a) Under Article 3(a) and (b) of [the SPC Regulation], may [an SPC] be granted for the substance protected by the basic patent (in this case, Protein D) where that substance has a therapeutic effect of its own (in this case, as a vaccine against the *Haemophilus influenzae* bacterium) but the marketing authorisation for the medicinal product does not relate to that effect?
>
> (b) Under Article 3(a) and (b) of [the SPC Regulation], may [an SPC] be granted for the substance protected by the basic patent (in this case, Protein D) where the marketing authorisation describes that substance as a 'carrier' for the actual active ingredients (in this case, pneumococcal polysaccharides), where the substance, as an adjuvant, enhances the effect of those substances, but where that effect is not expressly mentioned in the marketing authorisation for the medicinal product?"

47. The Court of Justice gave judgment without an Advocate General's opinion. It answered question 1 as follows:

> "23. '[P]roduct' is defined in Article 1(b) of Regulation No 469/2009 as 'the active ingredient or combination of active ingredients of a medicinal product'. However, the term 'active ingredient' is not defined in that regulation. That term also appeared in Article 1(b) of Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products (OJ 1992 L 182, p. 1), which was repealed by Regulation No 469/2009, and a question relating to that provision has already been referred to the Court. The Court held on that occasion that it is generally accepted in pharmacology that the term 'active ingredient' does not cover substances forming part of a medicinal product which do not have an effect of their own on the human or animal body (see judgment in *Massachusetts Institute of Technology*, EU:C:2006:291, paragraph 18).
>
> 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.
>
> 26. On the other hand, the Court has held that a substance which has no therapeutic effect of its own and which is used to obtain a certain pharmaceutical form of the medicinal product is not covered by the term 'active ingredient' and, consequently, cannot give rise to the grant of an SPC (judgment in *Massachusetts Institute of Technology*, EU:C:2006:291, paragraph 25).

> 27. The answer to the question whether a substance which is part of a medicinal product is an active ingredient within the meaning of Article 1(b) of Regulation No 469/2009 depends, therefore, on whether that substance has a pharmacological, immunological or metabolic action of its own, independently of any covalent binding with other active ingredients.
>
> 28. Accordingly, the answer to Question 1 is that Articles 1(b) and 3(a) of Regulation No 469/2009 must be interpreted as not precluding, in principle, the possibility that an active ingredient can give rise to the grant of an SPC where the active ingredient is covalently bound to other active ingredients which are part of a medicinal product."

48. The Court answered question 2(a) by holding that Article 3(b) "must be interpreted as precluding the grant of an SPC for an active ingredient whose effect does not fall within the therapeutic indications covered by the wording of the marketing authorisation". In this context, the Court referred to the SmPC for Synflorix and also to the European Public Assessment Report ("EPAR") prepared by the European Medicines Agency as part of the assessment of the application for the marketing authorisation for Synflorix (see [37]).

49. Finally, the Court considered question 2(b). It began by noting that it appeared from the SmPC for Synflorix that Protein D was neither an excipient nor an adjuvant, but rather a carrier protein ([42]-[44]). It therefore reformulated the question as asking whether "a carrier protein conjugated to a pneumococcal polysaccharide used in a vaccine for paediatric use may be regarded as a 'product' within the meaning of [the SPC Regulation], that is to say, as an 'active ingredient or combination of active ingredients of a medicinal product' ([45]). Given that Protein D did not have an immunogenic effect which was covered by the marketing authorisation for Synflorix, the question was therefore whether it "may be categorised as an 'active ingredient' where, conjugated with a polysaccharide antigen by means of a covalent binding, it produces such an effect" ([47]-[48]).

50. Having noted that there was nothing in the SPC Regulation which settled the matter and rejected Mr Forsgren's argument that an analogy could be drawn with Case C-11/13 *Bayer CropScience AG v Deutsches Patent- und Markenamt* [EU:C:2014:2010], the Court went on:

> "51. It is appropriate, consequently, to refer to the fundamental objective of Regulation No 469/2009, which is to ensure sufficient protection to encourage pharmaceutical research, which plays a decisive role in the continuing improvement in public health (judgment in *Georgetown University and Others*, EU:C:2011:776, paragraph 24 and the case-law cited).
>
> 52. In addition, as can be seen in particular from subparagraphs 4 and 5 of paragraph 28 of the Explanatory Memorandum to the Proposal for a Council Regulation (EEC) of 11 April 1990, concerning the creation of a supplementary protection certificate for medicinal products [COM(90) 101 final], the

> protection conferred by an SPC is largely intended to cover the cost of research leading to the discovery of new 'products'.
>
> 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."

51. As counsel for Abraxis emphasised, the questions in *Forsgren*, and hence the Court's answers, were about whether Protein D was itself an active ingredient within the meaning of the SPC Regulation, rather than about whether the polysaccharide antigens conjugated to Protein D were active ingredients.

Article 1(b)

*Summary of Abraxis' contentions*

52. Abraxis contends in summary as follows:

    i) nab-paclitaxel is a single active ingredient, rather than a combination of an active ingredient with an excipient or adjuvant, and it is a different active ingredient to paclitaxel, because in nab-paclitaxel paclitaxel is tightly bound to albumin, and this has important therapeutic consequences;

    ii) accordingly, nab-paclitaxel is a different "product" to paclitaxel within the meaning of Article 1(b), from which it follows that the Application complies with Article 3(d) because the Abraxane MA is the first authorisation to place nab-paclitaxel on the market;

iii) this conclusion is supported by the practice of the UK Intellectual Property Office of granting SPCs for pro-drugs (active ingredients which have been modified by the substitution of a covalently-bonded chemical group, usually with the purpose of improving its bioavailability) and PEGylated proteins (therapeutic proteins which have been modified by the addition of a polyethyleneglycol (PEG) moiety, again by covalent bonding, usually in order to prevent renal clearance, leading to a longer period of action) (Abraxis also relies upon an SPC granted in relation to a lipid complex product, but this was a long time ago and the facts are not entirely clear);

iv) it is also supported by a teleological interpretation of Article 1(b), since the purpose of the SPC Regulation is to compensate patent proprietors where the effective period of their monopoly is reduced by the time taken to obtain marketing authorisations for products protected by their patents, and hence to reward invention;

v) Abraxis accepts, however, that it is not clear that Article 1(b) should be interpreted as having the effect that nab-paclitaxel is a single active ingredient.

53. As counsel for the Comptroller pointed out, it is important to note that Abraxis argued before the hearing officer that, if nab-paclitaxel was not a single active ingredient, then it was a combination of active ingredients, but Abraxis has not pursued the latter argument on this appeal.

*Summary of the Comptroller's contentions*

54. The Comptroller contends in summary as follows:

i) the hearing officer found as a fact that nab-paclitaxel is not a single active ingredient, rather it is a combination of an active ingredient, namely paclitaxel, with a substance that is not an active ingredient, namely albumin, albeit that the latter is tightly bound to the former in the nanoparticles;

ii) this conclusion is supported by the terms of the Abraxane MA, the SmPC at Annex I of which identifies the composition in section 2 as "paclitaxel formulated as albumin bound nanoparticles" and the labelling at Annex III of which identifies the active substance in section 2 in precisely the same way, and of the EPAR for Abraxane which states in section 2.1 that "Abraxane is a cremaphor-free colloidal suspension of paclitaxel and human serum albumin. Abraxane is a new formulation developed to overcome the water insolubility of the active component paclitaxel …" and in section 2.2 that "Paclitaxel is a known active substance described in the Ph.Eur. and the USP";

iii) nab-paclitaxel stands in a different position to prodrugs and PEGylated proteins, both of which constitute different molecules to the drugs and proteins from which they are derived, and hence different active ingredients and different products, as can be seen from the marketing authorisations and SPCs in question;

iv) the law is clear and there is no need for a reference.

*Analysis*

55. In my judgment, it is clear that nab-paclitaxel is not the active ingredient of Abraxane within the meaning of Article 1(b) of the SPC Regulation: paclitaxel is the active ingredient and albumin is a carrier. It is not necessary to seek further guidance from the CJEU as to the interpretation of Article 1(b) since the interpretation of that provision is *acte éclairé*. My reasons are as follows.

56. First, it is clear from the judgments of the CJEU in *MIT*, *GSK* and *Forsgren* that Article 1(b) is to be interpreted narrowly and cannot cover a substance which does not itself correspond to an "active ingredient" or a "combination of active ingredients".

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.

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.

Article 3(d)

*Summary of Abraxis' contentions*

60. Abraxis contends in summary as follows:

    i) the CJEU held in *Neurim* that Article 3(d) was to be interpreted as meaning that the authorisation referred to in Article 3(b) was the first *relevant* authorisation, *i.e. the first authorisation within the scope of the basic patent*, to place the product on the market as a medicinal product;

ii) although *Neurim* was a case about a new *therapeutic use* of an old active ingredient, as Jacob LJ indicated in the judgment of the Court of Appeal at [28], the same policy considerations apply to a new *formulation* of an old active ingredient;

iii) Abraxis accepts, however, that it is not clear from *Neurim* that Article 3(d) should be interpreted in the same way in the case of a new formulation of an old active ingredient.

*Summary of the Comptroller's contentions*

61. The Comptroller contends in summary as follows:

i) the CJEU's decision in *Neurim* is confined to new therapeutic uses of old active ingredients;

ii) by contrast with its decision in *Neurim*, the CJEU has made it clear in *MIT*, *GSK* and *Forsgren* that SPCs cannot be obtained for new therapeutic formulations of old active ingredients;

iii) this distinction reflects the distinction drawn in paragraphs 11 and 12 of the Explanatory Memorandum.

*Analysis*

62. In my judgment it is not clear how far the reasoning of the Court of Justice in *Neurim* extends. As Abraxis acknowledges, on its face, the reasoning is limited to new therapeutic uses of old active ingredients. As Abraxis contends, however, it is arguable that the same policy considerations support Article 3(d) being interpreted in the same way in the case of new formulations of old active ingredients even if the therapeutic use is the same. This was certainly the view of Jacob LJ in the cases mentioned above. On the other hand, as the Comptroller argues, it appears from *MIT*, *GSK* and *Forsgren* that SPCs cannot be granted merely for new formulations. But since none of those decisions squarely addresses this issue, the position is not clear. Accordingly, I shall refer a question to the CJEU the substance of which is as follows:

> "Is Article 3(d) of the SPC Regulation to be interpreted as permitting the grant of an SPC where the marketing authorisation referred to in Article 3(b) is the first authorisation within the scope of the basic patent to place the product on the market as a medicinal product and where the product is a new formulation of an old active ingredient?"

63. In case it assists the Court of Justice, I will offer my own answer to this question. While I fully acknowledge the force of counsel for Abraxis' argument that the primary purpose of the SPC Regulation is to reward innovative research of the kind that led to the development of nab-paclitaxel and to compensate patentees for delays in obtaining marketing authorisations of the kind that Abraxis experienced with Abraxane, it must be recalled that the SPC Regulation was intended to provide a simple and predictable system that could be operated by the competent authorities of the Member States, and in particular the national patent offices, in a uniform manner.

Moreover, as discussed, the SPC Regulation aims to balance the interests of patentees with those of other stakeholders. To achieve those objectives, it is necessary to have bright-line rules even if they sometimes deprive meritorious inventions of extended protection. Article 1(b) is such a rule, and the Court of Justice has held that it should be strictly interpreted. In my view it would be inconsistent with a strict interpretation of Article 1(b) to interpret Article 3(d) as permitting SPCs to be obtained for new formulations of old active ingredients. If Article 3(d) were to be interpreted in that way, it would be likely to lead to uncertainty and inconsistency as to the circumstances in which SPCs for new formulations could be obtained, as the existing case law illustrates. For example, could an SPC be obtained where the basic patent protected a key ingredient in the new formulation other than the active ingredient (as in *MIT*, the first application in *GSK* and *Forsgren*), rather than the new formulation containing the active ingredient (as in the second application in *GSK* and the present case)? Moreover, I agree with the Comptroller that paragraphs 11 and 12 of the Explanatory Memorandum appear to indicate that SPCs should be available for new applications (i.e. new therapeutic uses) of old active ingredients, but not for new formulations. Accordingly, I would answer the question no.

Conclusion

64. For the reasons given above, I shall refer a question as to the interpretation of Article 3(d) of the SPC Regulation along the lines set out in paragraph 62 above. I shall hear counsel as to the precise wording of the question.