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Case Nos: HP-2016-000003/000024/000033

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Rolls Building
Fetter Lane, London, WC2A 2LL

Date: 21 March 2017

Before :

MR JUSTICE ARNOLD

- -

Between :

TEVA UK LIMITED **ACCORD HEALTHCARE LIMITED** **GENERICS (UK) LIMITED trading as MYLAN**	**Claimants**
- and -	
MERCK SHARP & DOHME CORPORATION	**Defendant**

- -
- -

Charlotte May QC and **Lindsay Lane** (instructed by **Pinsent Masons LLP**) for **Teva**
Charlotte May QC and **Kathryn Pickard** (instructed by **Taylor Wessing LLP**) for **Accord**
Charlotte May QC and **Joe Delaney** (instructed by **Taylor Wessing LLP**) for **Mylan**
Thomas Hinchliffe QC (instructed by **Hogan Lovells International LLP**) for **MSD**

Hearing dates: 2-3, 6 March 2017

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Judgment Approved

MR JUSTICE ARNOLD :

Contents

Introduction

1. In these proceedings the Claimants challenge the validity of the Defendant's ("MSD's") supplementary protection certificate SPC/GB08/022 ("the SPC") for a product described in the SPC as "A combination of efavirenz, emtricitabine or a pharmaceutically acceptable salt or ester thereof, and tenofovir or a pharmaceutically acceptable prodrug, salt or ester thereof, particularly tenofovir disoproxil, especially tenofovir disoproxil fumarate" ("the Product"). The SPC covers a product which is marketed by Bristol-Myers Squibb Co ("BMS") and Gilead Sciences Inc under the trade mark Atripla. Atripla is an anti-retroviral medication used in the treatment of human immunodeficiency virus (HIV). It is a combination product consisting of three active ingredients, namely (i) efavirenz (also known as EFV), (ii) tenofovir in the form of the disoproxil fumarate ("TDF") and (iii) emtricitabine (also known as FTC) in a single, fixed dose tablet. All three active ingredients are inhibitors of a viral enzyme known as reverse transcriptase.

2. The Claimants contend that the SPC does not comply with Article 3(a) or (c) 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").

3. The Claimants contend that the SPC does not comply with Article 3(a) because the Product is not protected by European Patent (UK) No. 0 582 455 ("the Patent"), which is relied upon by MSD as the basic patent for the SPC. It may be noted that MSD obtained the SPC by amending the Patent to insert claim 17 and relying upon claim 17 as protecting the Product, but MSD did not rely upon claim 17 at trial. Instead, MSD relied solely upon claim 16. I shall therefore ignore claim 17.

4. The Claimants contend that the SPC does not comply with Article 3(c) because MSD had previously obtained an SPC for efavirenz based on the Patent, namely SPC/GB00/35 ("the 035 SPC"), which expired on 19 November 2013. It is common ground that the Patent discloses and claims both a class of compounds which includes efavirenz and efavirenz itself specifically. Accordingly, the Claimants say that the Product has already been the subject of a certificate within the meaning of Article 3(c), which compensated MSD for the delay in exploiting the invention in the Patent as a result of the need to obtain a marketing authorisation for efavirenz.

5. The Claimants' primary case is that under Article 3(c). This is because the Claimants contend that the law with respect to Article 3(c) is clear. The Claimants' secondary case is that under Article 3(a). As will appear, this raises two issues of construction of claim 16. The Claimants say that, if either of those issues is resolved in favour of the Claimants, then again the law is clear. The Claimants accept, however, that if those issues are resolved in favour of MSD, then the issue which I recently considered in *Teva UK Ltd v Gilead Sciences Inc* [2017] EWHC 13 (Pat) and referred to the Court of Justice of the European Union for a preliminary ruling will arise again. MSD agrees with the Claimants as to the latter point, but does not agree that the law with respect to Article 3(c) is clear.

The marketing authorisations

6. The first marketing authorisation for efavirenz was granted on 20 November 1998. It is marketed by MSD under the name Stocrin (and also by BMS under the name Sustiva). The 035 SPC was based upon this marketing authorisation. Generic efavirenz has been available since expiry of the 035 SPC.

7. The first marketing authorisation for TDF was granted on 5 February 2002. It is marketed by Gilead in Europe under the name Viread.

8. The first marketing authorisation for emtricitabine was granted on 24 October 2003. It is marketed by Gilead in Europe under the name Emtriva.

9. Atripla was granted a marketing authorisation on 13 December 2007. The rationale for the product was described by the European Medicines Agency as follows:

> "The rationale for the fixed combination of efavirenz, emtricitabine and tenofovir DF is to simplify HIV-treatment regimens and to improve adherence to therapy by providing combination antiretroviral therapy for administration as a single, once-daily tablet. The individual active substances are already approved to be used together in combination therapy of HIV-1 infected patients."

The SPC Regulation

10. 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.

11. 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."

12. Articles 1, 3, 4 and 5 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 -

(a) the product is protected by a basic patent in force;

…

(c) the product has not already been the subject of a certificate;

…

Article 4

Subject-matter of protection

Within the limits of the protection conferred by the basic patent, the protection conferred by a certificate shall extend only to the product covered by the authorisation to place the corresponding medicinal product on the market and for any use of the product as a medicinal product that has been authorised before the expiry of the certificate.

Article 5

Effects of the certificate

Subject to the provisions of Article 4, the certificate shall confer the same rights as conferred by the basic patent and shall be subject to the same limitations and the same obligations."

Interpretation of the SPC Regulation

13. 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)."

14. 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 interests 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 Article 3(a)

15. I considered the interpretation of Article 3(a) in *Teva v Gilead* at [32]-[88]. I shall take that exposition as read and will not repeat it.

Interpretation of Article 3(c)

16. As is now widely recognised, the interpretation of Article 3(a) and the interpretation of Article 3(c) are both interdependent and dependent on the interpretation of Article 1(b). To date, the CJEU has adopted a fairly narrow interpretation of Article 1(b). In some cases, the CJEU has adopted a correspondingly narrow interpretation of Article 3(a), while in other cases it has adopted a broader interpretation. As the CJEU has recognised, the broader the interpretation of Article 1(b) and/or Article 3(a) that is adopted, the more important it becomes to adopt a narrow interpretation of Article 3(c) if the objectives of the SPC Regulation are not to be subverted.

17. In the Explanatory Memorandum which accompanied its Proposal for the predecessor to the SPC Regulation (COM(90) 101 final), the Commission of the European Communities stated:

> "35. It occurs very often that one and the same product is successfully granted several authorizations to be placed on the market, namely each time a modification is made affecting the pharmaceutical form, dose, composition, indications, etc. In such a case, only the first authorization for the product to be placed on the market, in the Member State in which the application is presented is taken into account for the purposes of the proposal for a Regulation, in particular for calculating the period of six months which the holder of the basic patent has to submit an application for a certificate. Furthermore, if the first authorization given is also the first authorization to place the product on the market in the Community, it serves as the only reference for all of the Member States for the purpose of calculating the duration of each of the certificates granted in each of the Member States for the same product (see Article B).

> 36. Lastly, the product must not have been the subject of a certificate in the Member State concerned. The certificate is designed to encourage research into new medicinal products so that the duration of protection by patent, is sufficient to enable the investments made in the research to be recovered. However, it would not be acceptable in view of the balance required between the interests concerned, for this total duration of protection for one and the same medicinal product to be exceeded. This might nevertheless be the case if one and the same product were able to be the subject of several successive certificates.
>
> This calls for a strict definition of the product within the meaning of Article 2. If a certificate has already been granted for the active ingredient itself, a new certificate may not be granted for one and the same active ingredient whatever minor changes may have been made regarding other features of the medicinal product (use of a different salt, different excipients, different pharmaceutical presentation, etc).
>
> In conclusion, it should be noted that, although one and the same product may be the subject of several patents and several authorizations to be placed on the market in one and the same Member State, the supplementary protection certificate will only be granted for that product on the basis of a single patent and a single authorization to be placed on the market, namely the first chronologically given in the State concerned (the first authorization in the Community being taken only to calculate a uniform duration of different certificates for one and the same product)."

18. In Case C-181/95 *Biogen Inc v SmithKline Biologicals SA* [1997] ECR I-357 SKB marketed Energix-B, a vaccine for Hepatitis-B virus, pursuant to licences granted under patents owned by both Biogen and the Institut Pasteur. Biogen applied for an SPC based on its patents after the Institute Pasteur had obtained an SPC based on its patent. In those circumstances the Tribunal de Commerce de Nivelles in Belgium asked whether, where a single medicinal product was covered by several basic patents, the predecessor to the Regulation precluded the grant of an SPC to each holder of a basic patent. The CJEU answered this question in the negative for the following reasons:

> "26. It must be borne in mind in that regard that the third and fourth recitals in the preamble give as a reason for the adoption of the Regulation the insufficient duration of the effective protection under the patent to cover the investment put into the pharmaceutical research. The Regulation thus seeks to make up for that insufficiency by creating a supplementary protection certificate for medicinal products, which may be obtained by the holder of a national or European patent under the same conditions in each Member State.

> 27. Article 6 of the Regulation confirms that the certificate is to be granted to the holder of the basic patent or his successor in title. Article 1(c) mentions the basic patents which may be designated for the purpose of the procedure for the grant of a certificate, namely those which protect a product as such, a process to obtain a product or an application of a product. The Regulation thus seeks to confer supplementary protection on the holders of such patents, without instituting any preferential ranking amongst them.
>
> 28. Consequently, where a product is protected by a number of basic patents in force, which may belong to a number of patent holders, each of those patents may be designated for the purpose of the procedure for the grant of a certificate. Under Article 3(c) of the Regulation, however, only one certificate may be granted for each basic patent."

19. The CJEU re-iterated this interpretation of the Regulation in *AHP*, another case in which there were multiple applications by different patentees for SPCs based on the same marketing authorisation for a single product.

20. These two cases clearly established that it was possible to obtain one SPC per basic patent per product where there were multiple patents covering one product. Prior to Case C-322/10 *Medeva BV v Comptroller-General of Patents, Designs and Trade Marks* [2011] ECR I-12051, it was generally thought that, by parity of reasoning, it was also possible to obtain one SPC per product per basic patent where one patent covered multiple different products.

21. In its judgment in *Medeva*, however, the Court of Justice held at [41]:

> " … where a patent protects a product, in accordance with Article 3(c) of Regulation No 469/2009, only one certificate may be granted for that basic patent (see *Biogen*, paragraph 28)."

This led some to conclude that it was only possible to obtain one SPC per patent even if the patent covered multiple products.

22. In Case C-484/12 *Georgetown University v Octrooicentrum Nederland* [EU:C:2013:828] Georgetown was the proprietor of a patent for a vaccine for the prevention of human papillomavirus (HPV) infection comprising L1 protein, or a fragment thereof, of HPV type 16 or type 18 or type 16 and type 18 together. Sanofi Pasteur had a marketing authorisation for Gardasil vaccine which contained a combination of HPV type 6, 11, 16 and 18 LI proteins. GSK had a marketing authorisation for Cervarix vaccine which contained a combination of HPV type 16 and type 18 L1 proteins. Georgetown filed a number of applications for SPCs relying on the authorisations for Gardasil and Cervarix. Two applications were granted by the Dutch Patent Office for the combination of types 6, 11, 16 and 18 and for the combination of types 16 and 18, but the Office refused one of the applications based on the Gardasil vaccine which defined the product as a single HPV L1 protein of type

16. Although the Office initially based its refusal upon Article 3(b), it subsequently relied upon Article 3(c) having regard to the SPCs which had already been granted.

23. In those circumstances the Rechtbank's-Gravenhage (District Court of The Hague) referred five questions to the CJEU, of which the first was as follows:

> "Does Regulation No 469/2009 …, more particularly Article 3(c) thereof, preclude, in a situation where there is a basic patent in force which protects several products, the holder of the basic patent from being granted a certificate for each of the protected products?"

24. In Case C-443/12 *Actavis Group PTC ehf v Sanofi* [EU:C:2013:833], [2014] RPC 20 Sanofi was the proprietor of a patent that covered an antihypertensive drug called irbesartan which expired on 20 March 2011. Irbesartan was marketed by Sanofi under the trade mark Aprovel. Sanofi obtained an SPC for "[irbesartan] optionally in the form of one of its salts" ("the Irbesartan SPC") based on the patent and marketing authorisations for irbesartan. The Irbesartan SPC expired on 14 August 2012. Sanofi also obtained an SPC for "[irbesartan] optionally in the form of one of its salts and hydrochlorothiazide" ("the Combination SPC") based on the patent and marketing authorisations for a fixed dose combination of irbesartan and hydrochlorothiazide which was marketed by Sanofi under the trade mark CoAprovel. The Combination SPC was due to expire on 14 October 2013. Actavis intended to market generic versions of both Aprovel and CoAprovel. It was common ground that the latter would infringe the Combination SPC if the Combination SPC was valid. Actavis contended that it was invalid on the grounds that (i) the Combination SPC was not protected by the patent within the meaning of Article 3(a) of the SPC Regulation and (ii) the product had already been the subject of an SPC (namely the Irbesartan SPC) contrary to Article 3(c) of the SPC Regulation or because the product had already been the subject of a marketing authorisation (namely the authorisations for Aprovel) contrary to Article 3(d) of the SPC Regulation.

25. While the *Georgetown* reference was pending, I referred questions to the CJEU concerning the interpretation of Article 3(a) and Article 3(c). Question 2 was as follows:

> "In a situation in which multiple products are protected by a basic patent in force, does Regulation [No 469/2009], and in particular Article 3 preclude the proprietor of the patent being issued a certificate for each of the products protected?"

26. *Georgetown* and *Actavis v Sanofi* were both heard by the Third Chamber of the CJEU, which gave judgment in both cases without an Advocate General's opinion on the same day. In both judgments, the Court of Justice held that (*Georgetown* at [30] and *Actavis v Sanofi* at [29]):

> "… it is possible, in principle, on the basis of a patent which protects several different 'products', to obtain several SPCs in relation to each of those different products, provided, inter alia, that each of those products is 'protected' as such by that 'basic patent' within the meaning of Article 3(a) of Regulation

> No 469/2009, in conjunction with Article 1(b) and (c) of that regulation …"

27. In *Actavis v Sanofi* the Court interpreted question 2 as asking, in essence, whether:

> "… in circumstances such as those in the main proceedings, in which, on the basis of a patent protecting an innovative active ingredient and an MA for a medicinal product containing that ingredient as the single active ingredient, the holder of that patent has already obtained an SPC for that active ingredient, Article 3(c) of Regulation No 469/2009 must be interpreted as precluding the holder of that patent from obtaining, on the basis of that same patent but an MA for a different medicinal product containing that active ingredient in combination with another active ingredient which is not protected as such by the patent, a second SPC relating to that combination of active ingredients."

28. The Court answered that question in the negative for reasons which were encapsulated in the following passages in its judgment:

> "30. … in circumstances such as those in the main proceedings, even if the condition laid down in Article 3(a) of Regulation No 469/2009 were satisfied, for the purpose of the application of Article 3(c) of that regulation, it cannot be accepted that the holder of a basic patent in force may obtain a new SPC, potentially for a longer period of protection, each time he places on the market in a Member State a medicinal product containing, on the one hand, the principle active ingredient, protected as such by the holder's basic patent and constituting, according to the statements of the referring court, the core inventive advance of that patent, and, on the other, another active ingredient which is not protected as such by that patent.
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> …
>
> 40. Bearing in mind the objective of Regulation No 469/2009, as referred to at paragraph 31 above – namely, to compensate the patent holder for the delay to the commercial exploitation of his invention by providing him with an additional period of exclusivity – first, the grant of the first SPC in respect of the single active ingredient irbesartan has already afforded the holder such compensation and, second, the objective of that regulation is not to compensate the holder fully for the delay to the marketing of his invention or to compensate for such delay in connection with the marketing of that invention in all its possible forms, including in the form of combinations based on that active ingredient.
>
> 41. It should be recalled that the basic objective of Regulation No 469/2009 is to compensate for the delay to the marketing of what constitutes the core inventive advance that is the subject

> of the basic patent, namely, in the main proceedings, irbesartan. In the light of the need, referred to in recital 10 in the preamble to that regulation, to take into account all the interests at stake, including those of public health, if it were accepted that all subsequent marketing of that active ingredient in conjunction with an unlimited number of other active ingredients, not protected as such by the basic patent but simply referred to in the wording of the claims of the patent in general terms, such as, in the case of the patent in the main proceedings, 'beta-blocking compound', 'calcium antagonist', 'diuretic', 'non-steroidal anti-inflammatory' or 'tranquilizer', conferred entitlement to multiple SPCs, that would be contrary to the requirement to balance the interests of the pharmaceutical industry and those of public health as regards the encouragement of research within the European Union by the use of SPCs.
>
> 42. It follows that, in such a situation, Article 3(c) of Regulation No 469/2009 precludes a patent holder from obtaining, on the basis of one and the same basic patent, more than one SPC in connection with irbesartan, since such SPCs would in fact be connected, wholly or in part, with the same product (see, to that effect, with regard to plant protection products, Case C-258/99 *BASF* [2001] ECR I-3643, paragraphs 24 and 27). On the other hand, if a combination consisting of an innovative active ingredient in respect of which an SPC has already been granted and another active ingredient, which is not protected as such by the patent in question, is the subject of a new basic patent within the meaning of Article 1(c) of that regulation, the new patent could, in so far as it covered a totally separate innovation, confer entitlement to an SPC for that new combination that is subsequently placed on the market."

29. In *Georgetown* the Court held the facts were to be distinguished from those in *Actavis v Sanofi* because the patent protected type 16 individually as well as the combinations. Accordingly, the Court held at [35]:

> "In the main proceedings, in the light of paragraph 30 above, the combination of the four active ingredients in question (which includes HPV-16) as well as HPV-16 as an active ingredient individually, are protected by Georgetown University's basic patent within the meaning of Article 3(a) of Regulation No 469/2009. Therefore, Article 3(c) of that regulation does not, in principle, preclude Georgetown University being granted, on the basis of that patent and the same MA, namely the marketing authorisation for Gardasil, an SPC both for the combination of active ingredients (HPV-6, HPV-11, HPV-16 and HPV-18) and for the active ingredient HPV-16 individually. Even if the protection conferred by two

such SPCs were to overlap, they would, in principle, expire on the same date."

30. In Case C-577/13 *Actavis Group PTC ehf v Boerhinger Ingelheim Pharma GmbH & Co KG* [EU:C:2015:165] Boehringer was the proprietor of a patent two of the claims of which covered telmisartan and one of its salts respectively. The patent expired on 31 January 2012. Boehringer marketed telmisartan under the trade mark Micardis. Boehringer obtained an SPC for telmisartan optionally in the form of a pharmaceutically acceptable salt ("the Telmisartan SPC") on the basis of the patent and a marketing authorisation for telmisartan. The Telmisartan SPC expired on 10 December 2013. Boehringer also obtained an SPC in respect of the combination of telmisartan and hydrochlorothiazide ("the Combination SPC") based on the patent and a marketing authorisation it had obtained for that combination. During the course of the application for the Combination SPC, Boehringer amended the patent to insert a new claim to the combination of telmisartan and hydrochlorothiazide. The Combination SPC was due to expire on 30 January 2017. Actavis contended that the Combination SPC was invalid on similar grounds to those raised in *Actavis v Sanofi* and also on grounds relating to the amendment of the patent.

31. Birss J referred four questions to the CJEU, questions 2 and 3 of which were as follows:

> "2. For the purposes of determining whether the conditions in Article 3 [of the SPC Regulation] are made out at the date of the application for an SPC for a product comprised of the combination of active ingredients A and B, where:
>
> (a) the basic patent in force includes a claim to a product comprising active ingredient A and a further claim to a product comprising the combination of active ingredients A and B, and
>
> (b) there is already an SPC for a product comprising active ingredient A ('Product X'),
>
> is it necessary to consider whether the combination of active ingredients A and B is a distinct and separate invention from that of A alone?
>
> 3. Where the basic patent in force 'protects' pursuant to Article 3(a) [of Regulation No 469/2009]:
>
> (a) a product comprising active ingredient A (Product X); and
>
> (b) a product comprising a combination of active ingredient A and active ingredient B ('Product Y');
>
> and where:
>
> (c) an authorisation to place Product X on the market as a medicinal product has been granted;
>
> (d) an SPC has been granted in respect of Product X; and

(e) a separate authorisation to place Product Y on the market as a medicinal product has subsequently been granted,

does … Regulation [No 469/2009], in particular Articles 3(c) and (d) and/or 13(1), preclude the proprietor of the patent being issued with an SPC in respect of Product Y? Alternatively, if an SPC can be granted in respect of Product Y, should its duration be assessed by reference to the grant of the authorisation for Product X or the authorisation for Product Y?"

32. The case was dealt with by a three-judge Chamber of the Court of Justice, all of whom had been members of the five-judge Chamber which had heard *Actavis v Sanofi* and *Georgetown*, and by the same rapporteur, again without an Advocate General's opinion. In its judgment the Court answered the second and third questions by holding that Articles 3(a) and (c) should be interpreted as precluding the grant of a second SPC to Boehringer for the combination of telmisartan and hydrochlorothiazide.

33. Having reiterated what it had said in *Acatvis v Sanofi*, the Court went on:

"38. It follows that, in order for a basic patent to protect 'as such' an active ingredient within the meaning of Articles 1(c) and 3(a) of Regulation No 469/2009, that active ingredient must constitute the subject-matter of the invention covered by that patent.

39. In the light of the foregoing considerations, the answer to Questions 2 and 3 is that Article 3(a) and (c) of Regulation No 469/2009 must be interpreted as meaning that, where a basic patent includes a claim to a product comprising an active ingredient which constitutes the sole subject-matter of the invention, for which the holder of that patent has already obtained an SPC, as well as a subsequent claim to a product comprising a combination of that active ingredient and another substance, that provision precludes the holder from obtaining a second SPC for that combination."

34. In my judgment it is clear from this case law that Article 3(c) precludes the grant of an SPC for a combination of active ingredients where one of those active ingredients embodies the "core inventive advance" or "sole subject-matter of the invention" of the basic patent and has already been the subject of an SPC based on that patent even if the patent contains one or more claims which protect the combination. On the other hand, it does not preclude the grant of an SPC for a combination of active ingredients, even if one of those active ingredients is protected by the basic patent and has already been the subject of an SPC, if the combination represents a distinct invention protected by the patent. If the combination is a distinct invention, it should not matter whether it is protected by the same patent or by a different patent.

The witnesses

35. Both sides called a medicinal chemist as an expert witness to educate the Court as to the common general knowledge of the person skilled in the art to whom the Patent is addressed. It is worth recording that the parties agreed to the sequential service of expert's reports, with MSD's expert's report being served first. This procedure appears to have worked well.

36. The Claimants' expert was Dr Andrew Spaltenstein. Dr Spaltenstein obtained a BS in Chemical Engineering from Winterthur Polytech in Switzerland in 1981, an MS in Chemistry from the University of Washington Seattle in 1984 and a PhD on the synthesis of oligo- and polynucleotides from the same University in 1988. In 1989 and 1990 he undertook post-doctoral research on the design and synthesis of anti-viral drugs at Harvard University. From 1990-2016 he was employed by companies in what is now the GlaxoSmithKline group ("GSK") successively as a Senior Research Scientist (1990-1995), Senior Research Investigator (1995-2000), Department Director, Antiviral Chemistry (2001-2006), Group Director, Antiviral Chemistry (2007-2008), Vice President, HCV Discovery Performance Unit (2008-2011) and Vice President, HIV Discovery Performance Unit (2012-2016). From 2015-2016 he was also an Adjunct Professor at the University of North Carolina, Chapel Hill, School of Pharmacy. Since 2016 he has been an independent consultant. He is an author of 61 published papers and a named inventor on 16 granted US patents.

37. In 1992 Dr Spaltenstein was working for what was then Burroughs Wellcome Co, which was a leading player in the field of antiviral, and in particular anti-HIV, drug development, having developed zidovudine (also known as 3'-azido-3'-deoxythymidine and AZT) and an expression system which made HIV protease available as a target enzyme for research.

38. Counsel for MSD made no criticism of Dr Spaltenstein as an expert witness, and accepted that he had done his best to assist the Court. Counsel nevertheless submitted that there were three factors that I should bear in mind in assessing Dr Spaltenstein's evidence.

39. First, counsel pointed out that Dr Spaltenstein's area of expertise in August 1992 was in the design and synthesis of potential inhibitors of proteolytic enzymes, including HIV protease. At that time, he had not worked on HIV reverse transcriptase. Dr Spaltenstein explained, however, that it was part of his job to be aware of the therapeutic area and of other potential targets as well.

40. Secondly, counsel submitted that it was difficult for Dr Spaltenstein accurately to remember the state of the art in August 1992 except where this was established by contemporaneous documentary evidence given that it was nearly 25 years ago. When this point was put to Dr Spaltenstein, he acknowledged it. Nevertheless, he went on to explain that it was an exciting time in the field and that, when he had re-read the contemporary literature when preparing his report, he found that he remembered many of the articles quite vividly. Moreover, no significant error in Dr Spaltenstein's recollection was demonstrated.

41. Thirdly, counsel pointed out that Dr Spaltenstein had been aware of information that was internal to GSK at the time, which would not have been common general knowledge. This was a point which Dr Spaltenstein made clear that he was alive to, however.

42. MSD's expert was Professor Katherine Seley-Radtke. Prof Seley-Radtke obtained an AS degree in Chemistry from St Petersburg Jr College in 1983. In 1990 she enrolled in a combined Bachelors and Masters programme at the University of South Florida which enabled her to obtain a BA in Chemistry in May 1992 after starting work on what became her doctoral research. In 1996 she obtained a PhD on the design and

synthesis of carbocylic nucleosides from Auburn University. From 1996-1998 she was a post-doctoral research fellow at the same university. From 1998 to 2003 she was Assistant Professor of Chemistry and Biochemistry at Georgia Institute of Technology. From 2003-2011 she was Associate Professor of Chemistry and Biochemistry at the University of Maryland, Baltimore and since 2011 she has been Professor of Chemistry and Biochemistry in the same institution. She is an author of 72 published papers, four reviews and five book chapters and a named inventor on three US patents or patent applications. She is the Immediate Past President of the International Society of Nucleosides, Nucleotides and Nucleic Acids, and she has received a number of awards and distinctions. One of the disease areas that has been the subject of her research is HIV.

43. Counsel for the Claimants made no criticism of Prof Seley-Radtke as an expert witness, and accepted that she had done her best to assist the Court. Counsel nevertheless submitted that Prof Seley-Radtke was not representative of the person skilled in the art to whom the Patent was addressed since she had only just started her doctoral research in August 1992 and was not working on HIV at that time (although she had attended meetings in which HIV was discussed). I accept this submission. Indeed, Prof Seley-Radtke did not in August 1992 satisfy her own definition in her first expert report of the qualifications of the skilled person, namely a PhD in organic chemistry and/or medicinal chemistry with a focus on drug design plus 3-5 years' practical experience including in the design and synthesis of nucleosides/nucleotides. Counsel for the Claimants further submitted that, to the extent that there were differences between them, I should give more weight to the evidence of Dr Spaltenstein. Again, I accept this submission.

44. I would add that counsel for the Claimants criticised Prof Seley-Radtke for confirming on oath her second expert report when, as Prof Seley-Radtke knew from reading a bundle of cross-examination documents supplied to her the day before, it contained an inaccurate statement (see further paragraphs 131-132 below). Counsel for MSD took responsibility for this, however, acknowledging that he should have asked the witness to correct that passage in her report before asking her to confirm it. This is something that happens too often in the Patents Court. Advocates who call expert witnesses should not forget that, when they ask an expert to confirm the accuracy of their report, they are asking the witness to confirm its accuracy at that moment, not what the witness believed to be accurate at the time the report was written. It not infrequently happens that a statement which an expert believes to be accurate when their report is written turns out later not to be accurate, or not to be accurate without qualification. In those circumstances the expert has a responsibility to correct it, but so too do the lawyers, since they understand the procedure whereas the witness usually does not.

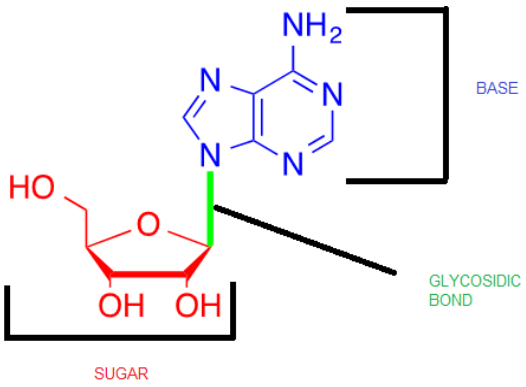
45. MSD also relied upon a witness statement from Dr Véronique Walsh of BMS. She gave evidence about the marketing authorisation history for efavirenz, TDF and emtricitabine as single actives and the combination products, although she did not herself have first-hand knowledge of those matters. The Claimants did not require her to attend for cross-examination.

Technical background

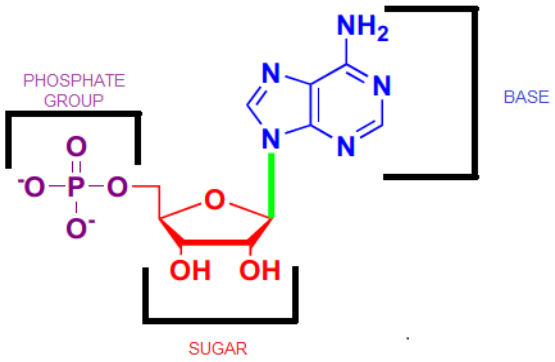
DNA and RNA

46. Deoxyribonucleic acid or DNA is a molecule that carries genetic information. DNA has a double helix structure often referred to as a "ladder". Sugar and phosphate moieties make up the sides (or the "sugar-phosphate backbone"). Complementary pairs of bases make up the rungs. There are four different bases – adenine (A), cytosine (C), guanine (G) and thymine (T).

47. When a base is linked to a five-carbon sugar (either ribose or deoxyribose), the base and sugar together are called a nucleoside. The base and the sugar moiety are linked by a glycosidic bond. Thus the structure of the nucleoside adenosine, which incorporates the base adenine, is as shown below.



48. When one or more phosphate groups is added to the nucleoside, the molecule is then referred to as a nucleotide. A phosphate group is a phosphorus atom (P) bonded to four oxygen atoms (O). Thus the structure of the nucleotide adenosine monophosphate is as shown below



49. The basic building blocks of DNA are nucleotides i.e. one of the four bases + a sugar + a phosphate group. A free, unincorporated nucleotide that is used to form DNA contains a chain of three phosphate groups. It can also be referred to as a nucleoside triphosphate. As it is being incorporated into DNA, the nucleoside triphosphate loses two of these phosphate groups, so that a nucleotide with only one phosphate group (referred to as a "monophosphate") is what is ultimately incorporated into the strand of DNA. These nucleotide building blocks are linked together by covalent bonds between the 3-OH' group of the deoxyribose sugar of one nucleotide and the

phosphate group of the next nucleotide to form a nucleic acid strand. The two strands are then linked by hydrogen bonds between the pairs of bases (A and T, C and G) to form the double helix.

50. The two strands of the DNA molecule are anti-parallel; they run in opposite directions. The ends of each DNA strand are referred to as the 5' end (where there is a phosphate group) and the 3' end (where there is a deoxyribose moiety). Each DNA molecule has a "leading" strand which runs in the 5' to 3' direction and a "lagging" strand which runs in the 3' to 5' direction.

51. The genetic material of HIV is in the form of RNA (ribonucleic acid) rather than DNA. Like DNA, RNA is comprised of a chain of nucleotides. Unlike DNA, RNA more often exists as a single strand folded onto itself, rather than being double stranded. In RNA, the thymine base (T) is replaced by a different base, uracil (U), which also pairs with adenine.

DNA synthesis

52. DNA synthesis is the process by which copies of the nucleic acid strands are made. The basic steps in normal DNA replication are as follows:

    i) The double helix structure is unwound and unzipped. An enzyme breaks the hydrogen bonds between the complementary pairs of bases which are holding the two strands of the parental DNA together. This process occurs at several locations on a DNA molecule and it leaves the A, C, G and T bases of each strand exposed.

    ii) Free nucleotides (base + sugar + phosphate) in their triphosphate forms, which are found in the nucleoplasm (the substance of the cell nucleus), bind to the exposed bases to form a new double stranded DNA molecule. The enzyme DNA polymerase epsilon (ε) binds to the leading strand and moves along it adding the free nucleotides in a 5' to 3' direction. The same base pairing rules apply as in the parental DNA (A+T and C+G).

    iii) DNA polymerase can only add DNA nucleotides in a 5' to 3' direction, not in a 3' to 5' direction. Therefore, synthesis of the lagging strand is done in fragments using a molecule of a second type of DNA polymerase – polymerase delta (δ). The fragments are then sealed together by an enzyme called ligase.

    iv) Once the two new strands are complete, they naturally twist to form a double helix. Each new double helix consists of one old and one new nucleic acid strand.

Reverse transcription

53. A crucial step in the process of HIV virus replication is reverse transcription, where reverse transcriptase (a viral DNA polymerase enzyme) copies the single stranded viral RNA into complementary double stranded viral DNA. Once the double stranded viral DNA has been integrated in to the host cell, it will be replicated in the usual way following the DNA replication steps set out above.

HIV and AIDS

54. HIV is a lentivirus (a subgroup of the retrovirus family) that causes Acquired Immune Deficiency Syndrome (AIDS). The retrovirus family consists of viruses whose genetic material is ribonucleic acid (RNA) rather than deoxyribonucleic acid (DNA). HIV primarily targets and infects key cells of the immune system which express the CD4 receptor molecule on their surface, including CD4+ cells (often called T-cells or T-helper cells), a type of white blood cell which are a crucial part of the human immune system.

55. AIDS is caused by HIV. However, AIDS is not synonymous with HIV infection and a person can be infected with HIV without having symptoms or a dangerously low CD4+ cell count. AIDS is essentially a very advanced stage of HIV infection when the immune system is no longer functioning. A person infected with HIV is deemed to have developed AIDS when their CD4+ cell count drops below 200 cells per millilitre of blood.

56. As the number of CD4+ cells in the body drops, the body's ability to deal with opportunistic infections is reduced. Examples of opportunistic infections often seen in patients with AIDS are tuberculosis, pneumonia, Kaposi's sarcoma and lymphoma (the latter two being types of cancer).

57. The basic steps in the replication cycle for HIV are as follows:

    i) HIV attaches to the surface of the host cell, and then enters the host cell (attachment and entry).

    ii) Viral RNA serves as a template and is reverse transcribed into a complementary DNA copy by the HIV reverse transcriptase enzyme (reverse transcription).

    iii) The viral double stranded DNA is transported into the nucleus and integrated into the host cell's genome by HIV integrase (integration).

    iv) Once integrated into the host's DNA, the viral DNA is transcribed into HIV messenger RNA, which is then translated into an immature form of HIV proteins, which are stuck together in the form of a long chain (transcription/translation).

    v) Each one of the HIV proteins is cut from the long chain by HIV protease. This creates the mature, active form of the protein (virus assembly).

    vi) The mature viral particles then "bud" and are released from the host cell through the membrane and go on to infect other host cells, thereby completing the virus life cycle (budding and maturation).

Antiretrovirals for treatment of HIV

58. The AIDS epidemic was first recognised in 1981. By 1983 the HIV virus had been identified and scientists and clinicians sought to develop effective treatments. By 1992 the key targets for researchers trying to find treatments for HIV were the reverse transcriptase and protease enzymes. Integrase was also targeted to a lesser extent.

59. The first antiretroviral to be developed for the treatment of HIV was AZT, which was authorised in the USA in 1987. AZT is a nucleoside reverse transcriptase inhibitor or NRTI. NRTIs are explained further below.

60. By August 1992 there were three approved drugs for the treatment of HIV in the USA, all of which were NRTIs. They were AZT, didanosine (also known as 2′-3′-dideoxyinosine or as ddI) and zalcitabine (also known as 2′-3′-dideoxycytidine or ddC). Only AZT was approved in the UK at that time. Another NRTI called stavudine (also known as d4T) was also in development.

61. It was known that these drugs had significant limitations. In particular:

    i) Efficacy: whilst these drugs were potent enough to bring about initial viral suppression in many patients, they led to only partial suppression and thus had limited durability in the majority of patients.

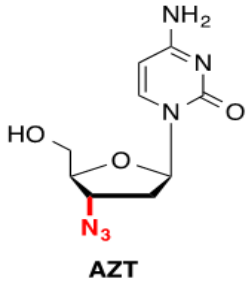
    ii) Durability of suppression: durability is related to efficacy and resistance. A partially suppressed virus will quickly mutate and become resistant to the drug and the drug effect will be reduced. By August 1992, it was known that HIV quickly developed resistance to NRTIs.

    iii) Toxicity: the first generation of NRTIs caused significant side-effects, ranging from vomiting, fevers, dizziness and confusion to long-term effects such as lipodystrophy or bone-loss. However, reducing the dose increased the risk of incomplete viral suppression and therefore the development of resistance.

62. In addition to NRTIs, other classes of antiretrovirals were also in clinical development by August 1992. It had been recognised that it would be beneficial to target different modes of action for the inhibition of enzymes involved in the replication of HIV. These included non-nucleoside reverse transcriptase inhibitors or NNRTIs (although they were not generally called NNRTIs at that time) and protease inhibitors (or PIs).

NRTIs

63. NRTIs are nucleoside analogues, i.e. a nucleoside (a base and sugar linked by a glycosidic bond) which has been structurally modified in some way. For example, in AZT the 3-OH' group in the deoxyribose ring of thymidine has been replaced with an azide group (N_3^-), as shown below.



AZT

64. It is this structural modification which leads to AZT's mechanism of action against HIV, which is “chain termination”. As explained above, usually the 3-OH' group of one nucleotide forms a covalent bond with the phosphate group of the next nucleotide

in the DNA chain. In NRTIs which lack a 3-OH' group on the deoxyribose moiety, this structural modification means that the phosphate group of the next incoming nucleotide in the DNA chain cannot link to the NRTI. As a result, the DNA chain stops growing.

65. Although it is the nucleoside analogue that is administered to the patient, it is not active against HIV in that form. The nucleoside analogue is not active until it has been converted to the active triphosphate form in a process known as phosphorylation. This process takes place within the cells of the body by cellular kinases (enzymes which add phosphate groups onto the 5-OH' group of the nucleoside, and subsequently the mono- and diphosphate groups). It is not possible to administer the active triphosphate form of a nucleoside analogue directly to a patient because it is too polar (i.e. too highly charged) to cross the phospholipid layer in the cellular membrane. It will be repelled by the hydrophobic part of the phospholipid molecules in the membrane.

66. The success of nucleoside analogues depends on at least three factors:

    i) the administered nucleoside analogue must be able to enter the target cells;

    ii) the nucleoside analogue must be recognised and processed in the cell by several human kinase enzymes; and

    iii) the reverse transcriptase enzyme must recognise and incorporate the triphosphate form of the drug candidate into the growing DNA/RNA chain, at which point it acts as a chain terminator.

NNRTIs

67. NNRTIs are structurally different from nucleosides, hence the name "non-nucleoside". They do not even resemble each other in terms of their structure. In August 1992 the precise mechanism of action of NNRTIs was not fully understood. What was known was that they also inhibit reverse transcriptase, but work by a different mechanism from NRTIs.

68. Whilst no NNRTIs had been approved as medicines by August 1992, at least five chemically distinct classes of NNRTIs were in development. Clinical efficacy studies in HIV patients had been conducted for compounds called TIBO, BI-RG-587 (subsequently known as nevirapine), L-697,661 and U87201, but the results were generally disappointing because resistance developed so quickly that little or no antiviral efficacy was observed.

Treatment of AIDS

69. In addition to viral suppression with antiretroviral drugs, additional approaches were pursued in order to address directly the symptoms of AIDS. Thus, a patient presenting with AIDS was almost always treated with a combination of antiretrovirals and other anti-infectives (e.g. antifungals, antibacterials), or anticancer drugs, depending on the specific presence of co-morbidities.

Resistance to HIV drugs

70. In August 1992 resistance was known to be a major problem when treating HIV. Resistance occurs because the virus replicates so rapidly that mutations are common. Drug resistance is caused by changes (mutations) in the genetic structure of the virus which can result in alterations to certain proteins, most commonly enzymes, which help HIV replicate. Since the biological activity of a drug is based on structural interactions between the binding site of the enzyme and the drug, changing those interactions also changes the activity of the drug. Once the mutation has occurred, the mutated version of the virus is copied and it then becomes the dominant strain in that patient.

71. Inhibition of the virus is never 100% and, as a result, resistance can develop because complete inhibition of the replication pathway is not achieved. This can be exacerbated by poor patient compliance.

72. In 1992 cross-resistance was also known to be a problem. That occurs when resistance to one HIV drug causes resistance to other drugs in the same class.

73. By August 1992, resistance to AZT was already prevalent and a body of published literature on the problems of resistance was already in existence. Resistance had also developed to ddI, less than a year after it had been approved by the US Food and Drug Administration. As noted above, it was known that resistance had developed very quickly to all the NNRTIs which were under investigation.

74. At that time, the skilled person would have been aware of three strategies to overcome the problem of HIV resistance:

    i) increase the dose of the failing drug, which can work in certain circumstances, but often has limited success due to toxicity concerns at higher doses;

    ii) find a new drug with a different resistance profile; or

    iii) combine two or more drugs, if possible with complementary resistance profiles.

Combination therapy

75. In August 1992, because monotherapy for HIV was failing as a result of resistance, combination therapy was also being considered. When two or more agents are given in combination there can be one of four interactions:

    i) indifferent – the result is equal to the result of the most effective drug by itself;

    ii) antagonistic – the result is significantly worse than the indifferent response;

    iii) additive – the result is equal to the combined action of each drug used separately; or

    iv) synergistic – the result is significantly better than the additive response.

76. The theory behind combination therapy for HIV was that, by targeting the replication pathway of HIV at two different steps or using drugs that had different mechanisms of action on the same enzyme, the chances of inhibiting replication are increased, and hence the chances of developing resistance are reduced. Combination therapy was also thought to have a number of other potential advantages, including the potential to allow lower doses and thus reduce toxicity and increase patient compliance.

77. The idea of combination therapy was accepted as a basis for further investigation in August 1992, and interest in combinations of HIV drugs was growing. The motivation to combine different drugs was described by Prof Seley-Radtke in her first report in the following terms:

> "In 1992, researchers and clinicians were desperate to find improved treatments for HIV which was essentially still a death sentence at that time. Those working in the field were trying everything in an effort to find something that worked."

The Patent

78. The Patent was applied for on 3 August 1993 with an earliest claimed priority date of 7 August 1992. It is entitled "Benzoxazinones as inhibitors of HIV reverse transcriptase". It was granted on 2 November 2000 and expired on 2 August 2013.

79. The specification begins by briefly introducing HIV, reverse transcriptase and reverse transcriptase inhibitors. It then states at [0003]:

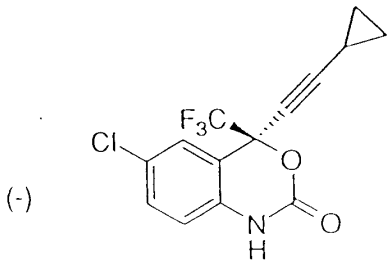
> "Applicants demonstrate that the compounds of this invention are inhibitors of HIV reverse transcriptase. The particular advantage of the present compounds are their demonstrated inhibition of resistant HIV reverse transcriptase."

80. After acknowledging two items of prior art, the specification continues at [0006]:

> "Compounds of formula I, as herein defined, are disclosed. These compounds are useful in the inhibition of HIV reverse transcriptase (and its resistant varieties), the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV using compounds of formula II are also disclosed."

81. Formula I and formula II are Markush formulae which are set out at [0009] and [0007] respectively. At [0010]-[0011] the specification identifies Compound 37.2 as being the most preferred compound of the invention. This compound is also referred to in the Patent as L-743,726. (The fact that these names refer to the same compound

appears from [0074]). It is efavirenz. The chemical structure of efavirenz as set out in the Patent is shown below.



82. A number of other compounds of the invention are specifically illustrated at [0012]-[0018] and in Tables 1 and 2. These tables span 12 pages of the specification.

83. Thereafter, the specification provides further general details about the compounds of the invention, including in relation to chirality and the terms used in the general formulae at [0020]-[0024]. It then goes on to describe in some detail suitable methods for synthesizing the compounds of the invention at [0025]-[0034]. A method for the synthesis of L-743,726 (i.e. efavirenz) is referred to at [0033] and described more fully later in the specification as Example 6 at [0071]-[0074].

84. The specification describes uses of the compounds of the invention at [0035]-[0037]. At [0036] it states that the compounds are "useful in the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS". At [0037] it states that the "particular advantage" of the compounds is their "potent inhibition against HIV reverse transcriptase rendered resistant to other antivirals, such as L-697,661, which is 3-([(4,7-dichloro-1,3-benzoxazol-2-yl)methyl]-amino)-5-ethyl-6-methyl-pyridin-2(1H)-one; or L-696,229, which is 3-[2-(1,3-benzoxazol-2-yl)ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one; or AZT". L-697,661 and L-696,229 are two NNRTIs.

85. The specification next describes various methods of administration of the compounds and medicinal preparations at [0038]–[0045]. In this context, it states in [0045]:

> "For combination therapy with nucleoside analogs, a preferred dosage range is 0.1 to 20 mg/kg body weight for the compounds of this invention administered orally in divided doses, and 50 mg to 5 g/kg body weight for nucleoside analogs administered orally in divided doses."

86. Discussion of combinations begins at [0046]:

> "The present invention is also directed to combinations of the HIV reverse transcriptase inhibitor compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals,

> immunomodulators, anti-infectives, or vaccines, such as those in the following Table"

87. The table that follows spans eight pages and is sub-divided into the following headings: "Antivirals"; "Immuno-modulators"; "Anti-infectives"; and "Other". AZT, d4T, ddI and ddC are listed in the Antivirals section, together with L-697,661 and L-696,229 and other compounds. Emtricitabine and tenofovir are not mentioned.

88. The specification then states at [0047]:

> "It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS. For example, a compound of Formula I or Formula II may be suitably administered in combination with a nucleoside analog having known biological activity against HIV reverse transcriptase. Appropriate nucleoside analogs are generally chain terminators and include AZT, ddC, ddI, d4T, HEPT and 3'-fluoro-2',3'-dideoxythmidine".

89. At [0048]-[0052] the specification identifies methods of synthesis of the nucleoside analogues referred to in the last sentence of [0047] and of L-697,661 and L-696,229.

90. At [0053] the specification states:

> "Preferred combinations are simultaneous, intermittent, or alternating treatments of L-743,726 [i.e. efavirenz] with or without an inhibitor of HIV protease. An optional third component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, ddc or ddI. A preferred inhibitor of HIV protease is L-735,524. Other preferred inhibitors of HIV reverse transcriptase include L-697,661. These combinations may have synergistic effects on limiting the spread of HIV. Preferred combinations include the following: (1) L-743,726 [efavirenz] with L-735,524, and, optionally any of L-697,661, AZT, ddI or ddC; (2) L-743,726 [efavirenz] and any of L-697,661, AZT, ddL or ddC. Pharmaceutically acceptable salts of these compounds are also included".

91. Example syntheses of compounds of the invention are described at [0054]-[0075]. As noted above, one of the examples describes the synthesis of efavirenz.

92. The specification then describes a reverse transcriptase assay and a cell spread assay (an assay that measures the inhibition of the spread of HIV in cell cultures) and sets out results of those assays for Compound 37.2 (i.e. efavirenz) together with some pharmacological data at [0076]-[0079].

93. From [0080] onwards, the specification describes tests done to determine the synergistic effect of a combination of efavirenz with: (i) ddI; (ii) AZT and (iii) L-735,524 (a PI). Table S (also referred to in the specification as Table 5) sets out the results of those tests. On their face, these appear to show that the most synergistic combination is efavirenz with AZT and the least synergistic combination is efavirenz with ddI, but no statistical information is included. The table also includes a triple combination of efavirenz, L-735,524 and AZT, but no result is given for that combination and there is no explanation for its absence.

The claims

94. Although the only claim in issue is claim 16, the Claimants contend that it is important to consider claim 16 in context, including the context provided by the preceding claims.

95. Claim 1 is to the use of a compound of formula II or a pharmaceutically acceptable salt thereof for the preparation of a medicament for inhibiting HIV reverse transcriptase, for preventing infection of HIV, for treating infection by HIV or for treating AIDS or ARC.

96. Claim 2 is to the use of claim 1 wherein the compound of formula II is one of five compounds, of which efavirenz is the first, or a pharmaceutically acceptable salt thereof.

97. Claim 5 is to a compound of formula I or a pharmaceutically acceptable salt thereof.

98. Claim 6 is to a compound which is one of five compounds, of which efavirenz is the first, or a pharmaceutically acceptable salt thereof.

99. Claim 7 is in the following terms:

> "A combination of a compound of Formula I as defined in claim 5 or Formula II as defined in claim 1 or 2 or a pharmaceutically acceptable salt thereof with a nucleoside analog having biological activity against HIV reverse transcriptase."

100. Claim 8 is as follows:

> "A combination of AIDS antiviral compounds which is L-734,726 [i.e. efavirenz] and L-735,524 and, optionally, one or more of the HIV inhibitors selected from the group consisting of L-697,661, AZT, ddI or ddC."

101. Claim 9 is as follows:

> "A combination of AIDS antiviral compounds which is L-734,726 [i.e. efavirenz] and one or more of the HIV inhibitors selected from the group consisting of L-697,661, AZT, ddI or ddC."

102. Claim 12 is to efavirenz or a pharmaceutically acceptable salt thereof.

103. Claim 13 is to a pharmaceutical composition comprising the compound of claim 12 (i.e. efavirenz) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

104. Claim 14 is to the compound of claim 12 or a pharmaceutically acceptable salt thereof for use in a method of therapy.

105. Claim 15 is to the use of efavirenz or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting HIV reverse transcriptase, for preventing infection of HIV, for treating infection by HIV or for treating AIDS or ARC.

106. Claim 16 is in the following terms:

> "A combination of the compound of claim 12 or a pharmaceutically acceptable salt thereof with a nucleoside analog having biological activity against HIV reverse transcriptase."

The person skilled in the art

107. There is little dispute as to the composition of the skilled team to which the Patent is addressed. It is common ground that it would be a skilled team led by a medicinal chemist, but also including a biochemist, a virologist, a formulation chemist and possibly a molecular biologist. There is a minor dispute as to whether it would also include a clinician, but neither side suggests this matters for present purposes. Since it is common ground that the skilled team would be led by the medicinal chemist and since both sides were able to deal with the issues arising in this case by calling solely a medicinal chemist as an expert witness, I shall for convenience refer to the skilled person rather than the skilled team.

The relevant date

108. As noted above, the earliest claimed priority date of the Patent is 7 August 1992. The Claimants have not challenged that claim to priority. It is well established that, where either there is no challenge to priority or any challenge is rejected, the validity of the claims of a patent must be assessed as at the priority date, and in particular in the light of the common general knowledge of the skilled person to whom the patent is addressed at that date. Consistently with that approach, both sides instructed their respective expert to consider the common general knowledge and the Patent as at August 1992. Neither side instructed their expert to consider the common general knowledge or the Patent as at any later date. Equally consistently with that approach, the skeleton arguments prepared by counsel for the Claimants and counsel for MSD for trial both addressed the issues in this case as at August 1992. There was no suggestion that any later date was relevant.

109. Despite this, counsel for MSD submitted in his closing submissions that the Patent and its claims should be construed as at the date of publication of the Patent, namely 2 November 2000. In support of this submission, he cited the statement of Stuart-Smith LJ to that effect in *Willemijn Houdstermaatschappij BV v Madge Networks Ltd* [1992] RPC 386 at 388. As counsel for the Claimants pointed out, however, that statement

was *obiter* since there does not appear to have been any issue as to the correct date in that case. Furthermore, counsel for MSD referred me to the discussion in *Terrell on the Law of Patents* at 9-27 to 9-33, in which the editors note that it was held in *Dyson Appliances Ltd v Hoover Ltd* [2001] RPC 26 at [48(k)] (Michael Fysh QC, as he then was) that the relevant date was the application date and recognise that the law is not settled, although they argue in favour of the publication date. As at present advised, I have to say that I do not find the editors' arguments convincing. I would add that it can be seen from reading decisions of this Court and the Court of Appeal over at least the past decade or two that the general practice is to construe patent claims as at the priority date (or the application date if priority is lost).

110. Be that as it may, I consider that it is not open to MSD to contend that the Patent should be construed as at any date later than 7 August 1992 in any event. This is for two related reasons. First, because MSD did not advance any such case prior to closing submissions and thereby deprived the Claimants of the ability to prepare to meet such a case. Secondly, because there is no proper evidential foundation for the exercise of construing the Patent as at any later date. Although there were a few stray references in the evidence to later developments, and in particular later developments concerning emtricitabine which counsel for MSD sought to fasten on to in his closing submissions, MSD did not put before the Court evidence as to the common general knowledge of the skilled person as at 2 November 2000, or any date later than 7 August 1992. That would have required MSD to ask Prof Seley-Radtke to consider and explain in her first expert report how the common general knowledge had changed between those dates, which would have enabled the Claimants to ask Dr Spaltenstein to consider the extent to which he agreed with that evidence. No such exercise was attempted.

Common general knowledge

111. There was no dispute between the parties as to the principles to be applied when determining whether or not something was common general knowledge, nor was there any dispute that everything I have set out under the heading "technical background" above was common general knowledge, but there were a number of areas of dispute as to what was common general knowledge applying those principles.

Emtricitabine

112. It is common ground that emtricitabine is a NRTI. The Claimants contend that it was not common general knowledge that it was active against HIV reverse transcriptase in August 1992. The evidence in this case is that its activity was first mentioned in a review article by Raymond Schinazi *et al*, "Insights Into HIV Chemotherapy", *AIDS Research and Human Retroviruses*, 8(6), 963-990 (June 1992) ("Schinazi"). Dr Spaltenstein's evidence was that this was not generally known in August 1992. Prof Seley-Radtke agreed with this in cross-examination.

113. Faced with this evidence, counsel for MSD did not contend in his closing submissions that it was common general knowledge that emtricitabine was active against HIV reverse transcriptase. He submitted, however, that it was important to apply a consistent standard when determining what was common general knowledge, and that if a single paper shortly before the priority date was not sufficient to make the activity of emtricitabine common general knowledge, then nor could a single paper shortly

before the priority date make other information common general knowledge. I accept that submission.

Tenofovir

114. It is common ground that tenofovir can be described as a nucleotide analogue, but MSD contends it is also a "nucleoside analog" within the meaning of claim 16. Leaving that dispute aside for the moment, it is common ground that it was not common general knowledge that tenofovir was active against HIV in August 1992. This was first described in the literature in 1993.

Combination therapy

115. The principal dispute between the parties concerns the extent of the skilled person's common general knowledge regarding combination therapy for HIV. There is no dispute that the matters I have set out in paragraphs 46-77 above were common general knowledge.

116. Nor is there any dispute that it was common general knowledge that combinations of AZT with ddC and with ddI had both demonstrated synergy *in vitro* and were undergoing clinical trials (and in the case of AZT with ddC had been approved in the USA). Although this is not in dispute, it is worth referring to three of the publications which show this.

117. The first is an article by Thomas Merigan, "Treatment of AIDS with Combinations of Antiretorviral Agents", *Am. J. of Med.*, 90 (suppl 4A), 8S-17S (10 April 1991), which began as follows (at 8S):

> "The treatment of acquired immunodeficiency syndrome (AIDS) is still virtually in its infancy. 3'-azido-3'—deoxythymidine (zidovudine, AZT), the current standard therapy, was first given to a patient with AIDS only 5 years ago. Now, new drugs of several different classes are being subjected to clinical trials singly and in various combinations with zidovudine. As the history of antibiotics and antineoplastic agents has demonstrated, combination therapy with several agents often is the most effective therapy. Combination therapy may actually result in equal or superior efficacy with reduced toxicity and a reduced requirement for each agent."

After discussing the rationale for combination therapy and agents proposed for combination therapy, the author went on to discuss a number of current clinical trials involving combination therapy, including trials of combinations of AZT with ddC and with ddI.

118. The second is an article by Victoria Johnson *et al*, "Two-Drug Combinations of Zidovudine, Didanosine and Recombinant Interferon-α Inhibit Replication of Zidovudine-Resistant Human Immunodeficiency Virus Type 1 Synergistically In Vitro", *J. Inf. Dis.*, 164, 646-55 (October 1991), which reported synergistic interaction between (among other combinations) AZT and ddI *in vitro*, and stated that clinical trials were underway. In the introductory part of the article the authors stated (at 646):

> "Despite the progress made in the development of single-agent therapy for HIV-1 infection, monotherapy with either AZT, ddI or interferon-α has been associated with drug toxicity or failure [17, 26-30]. In addition, AZT-resistant varieties of HIV-1 have been isolated from patients receiving AZT as extended single-agent therapy [31-37], although the clinical implications of these findings remain uncertain. It is likely that combined therapy will be required for effective long-term treatment of HIV-1 infection, as in the approach to certain other infectious diseases (e.g. tuberculosis) and cancers [38-42]. Anti-HIV-1 combination strategies that demonstrate favourable drug interactions (e.g. synergy) may allow the use of individual agents below their toxic concentrations, provide more complete viral suppression, and limit the emergence of drug-resistant HIV-1 mutants."

119. The third is an article by Tze-Chiang Meng *et al*, "Combination Therapy with Zidovudine and Dideoxycitidine in Patients with Advanced Human Immunodeficiency Virus Infection", *Annals of Int. Med.*, 116(1), 13-20 (January 1992), which reported the results of a combined Phase I and Phase II study (which had previously been presented in part at the Sixth International Conference on AIDS in San Francisco in June 1990) and concluded that "[c]ombination therapy with ddC and higher doses of [AZT] produced greater and more persistent effects in patients with advanced HIV infection compared with other study regimens and with the results of previous trials of [AZT] monotherapy". Near the end of this paper, the authors said (at 18-19):

> "Our data warrant expeditious investigation of combination regimens to increase efficacy and to reduce the complications that may be associated with the emergence of drug resistance. The ideal agents for use in combination regimens would be synergistic and have nonoverlapping toxicity profiles. Based on our data, initial testing of these combinations should include drug doses that provide the best therapeutic end individually. The prospect of creating antiretroviral compounds with different mechanisms of action now provides the promise of more effective long-term regimens to treat patients with HIV infection."

120. The dispute is as to the extent of the skilled person's common general knowledge with regard to combinations other than combinations of NRTIs. It is common ground that there had been a small number of published reports of *in vitro* tests of combinations of both a NRTI with a PI and a NRTI with a NNRTI, but there is a dispute as to the extent that this was common general knowledge. It is therefore necessary to consider the evidence on this point.

121. In paragraph 98 her first report, Prof Seley-Radtke stated that "the fact that a combination of NRTIs with a PI or an NNRTI was being tried would not have been CGK by August 1992".

122. Earlier in her first report, Prof Seley-Radtke had referred to and exhibited a chapter by Tony Mazzulli and Martin Hirsch entitled "Combination Therapy for HIV-1 Infection" in a book edited by James Mills and Lawrence Corey entitled *Antiviral Chemotherapy: New Directions for Clinical Application and Research*, volume 3, at 385-416 ("Mazzulli and Hirsch") as reflecting the common general knowledge at the priority date even though the book was not published until April 1993 (an assessment Dr Spaltenstein agreed with). In the introduction, Mazzulli and Hirsch stated:

> "Despite the ever increasing number of agents that have been described with activity against HIV-1, monotherapy of HIV-1 infection has met with only limited success. Recent reports describing HIV-1 isolates with reduced susceptibility to single agents following prolonged therapy of HIV-1 infection *in vivo* [1,2] and *in vitro* [3] have further raised concerns over the use of monotherapy for this infection. More recently, therefore, greater emphasis has been placed on the development and investigation of combination regimens for the treatment of HIV-1 infection.
>
> Combination chemotherapy is a therapeutic strategy that has been used successfully in the treatment of other diseases including bacterial sepsis, fungal and mycobacterial infections, and malignancies. In the treatment of HIV-1 infections, combination chemotherapy offers several potential advantages over monotherapy. …
>
> … Several studies, ranging from *in vitro* testing to clinical trials, have now been completed or are currently underway evaluating various multi-drug regimens for the treatment of HIV-1 infections."

123. The authors went on to list in Table 1 16 combinations of drugs which had been tested *in vitro* for efficacy against HIV. In 15 cases it was found that the combination was synergistic, while in one case it was antagonistic. Among the synergistic combinations listed were AZT and ddI (although this was a mistake – as can be seen both from the title of the reference cited, reference 43, and from the passage quoted below, the other NRTI was in fact ddC) with a PI identified as RO 31-8959 (now known as saquinavir). As the authors explained (at 391):

> "Because of its potent activity alone and the fact that Ro 31-8959 acts at a site different from the reverse transcriptase inhibitors, combinations of this agent with ddC and AZT were tested *in vitro* against both AZT-sensitive and AZT-resistant isolates [43]."

124. Reference 43 was an abstract of a presentation at a conference in San Diego in November 1991 which is not in evidence. As Prof Seley-Radtke noted in her first report, the results of this study were only fully published after the priority date in Victoria Johnson *et al*, "Human Immunodeficiency Virus Type 1 (HIV-1) Inhibitory Interactions between Protease Inhibitor Ro 31-8589 and Zidovudine, 2′-3′-Dideoxycytidine, or Recombinant Interferon-αA against Zidovudine-Sensitive or -

Resistant HIV-1 In Vitro", *J. Inf. Dis.*, 166, 1143-1146 (November 1992) ("Johnson 1992").

125. The authors went on to discuss other agents that had been tested in combination (at 393):

> "As the number of agents with activity against HIV-1 continues to grow, so has the number of combination regimens tested in vitro against HIV-1. However, insufficient data regarding the analysis of these drugs interactions have been provided in some of these studies for us to assess synergistic, additive or antagonistic effects *in vitro* (Table 4).
>
> Recently, interest has focused on a series of compounds known as dipyridodiazepinones [51,52] and TIBO compounds [53] which are potent inhibitors of HIV-1 RT but not HIV-2 RT. Activity of these compounds appears to be mediated through non-competitive binding at a site separate from the template or nucleoside binding sites on the RT molecule [51, 53]. AZT-susceptible and AZT-resistant isolates of HIV-1 appear to be equally susceptible to these agents. The combination of BI-RG-587 [now known as nevirapine], a dipyridodiazepinone, and AZT were shown to be synergistic in vitro against a laboratory strain of HIV-1 [54]. These encouraging results have led to the early institution of combination clinical trials of these compounds with AZT."

126. In their conclusion, the authors stated (at 402):

> "The chronic nature of HIV-1 infection, which necessitates the use of prolonged continuous therapy, coupled with the emergence of AZT-resistant mutants following extended monotherapy with AZT, suggests that future advances in the treatment of HIV-1 infection lies in the use of combination chemotherapy. Although *in vitro* efficacy against HIV-1 may not necessarily correlate with *in vivo* efficacy, properly and carefully controlled laboratory studies form an essential first step in the evaluation of potentially useful combination regimens. …
>
> It is difficult to predict what future regimens for HIV infection will be effective and widely utilized. However, it appears likely that such regimens will include several agents in combination, in sequence, or in sequential combinations. Future clinical trials based on promising leads from the laboratory should result in more effective combination therapy in the years ahead."

127. Prof Seley-Radtke stated in her first report that she had only found one paper reporting a combination of a NRTI with a PI and one paper reporting a combination of a NRTI with a NNRTI published before 7 August 1992, copies of which she exhibited:

i) Seiji Kageyama *et al*., "In Vitro Inhibition of Human Immunodeficiency Virus (HIV) Type 1 Replication by C_2 Symmetry-Based HIV Protease Inhibitors as Single Agents or in Combinations", *Antimicrobial Agents and Chemotherapy*, 36(5), 926-933 (May 1992). This reported that combinations of AZT or ddI (NRTIs) with three PIs were synergistic or additive. I also note that the authors stated (at 931):

> "A] logical extension of current approaches for the therapy of HIV infections would be the use of combinations of multiple antiviral agents which have different antiretroviral mechanisms … Such combination therapy may enhance the antiretroviral activity and reduce the adverse effects of each drug. In addition, the development of drug-resistant HIV variants may also be delayed with the combined use of multiple drugs versus the use of single drugs."

ii) Douglas Richman *et al*, "BI-RG-587 Is Active against Zidovudine-Resistant Human Immunodeficiency Virus Type 1 and Synergistic with Zidovudine", *Antimicrobial Agents and Chemotherapy*, 35(2), 305-308 (February 1991) ("Richman"), which is reference 54 in Mazzulli and Hirsch. Richman reported that the combination of AZT (a NRTI) and nevirapine (a NNRTI) is synergistic. Again, I also note that the authors stated (at 307):

> "Combination chemotherapy for HIV infection has been contemplated to increase efficacy and permit lower doses to reduce toxicity, as well as to reduce the likelihood of the emergence of drug resistance …"

128. In his report Dr Spaltenstein disagreed with the statement from paragraph 98 of Prof Seley-Radtke's first report that I have quoted in paragraph 121 above. He accepted that there were no clinical trials of combinations of NRTIs with either PIs or NNRTIs in August 1992, but said that *in vitro* data relating to such combinations were being generated and published. In support of this, he referred to three of Prof Seley-Radtke's exhibits, namely Johnson 1992, Richman and (the studies referenced in) Mazzulli and Hirsch, which he said would have been widely read and absorbed within weeks of publication. (As noted above, however, Johnson 1992 was published several months after the priority date.) He expressed the opinion that it was routine to consider such combinations in August 1992.

129. Dr Spaltenstein did not exhibit any additional publications reporting *in vitro* data for combinations of NRTIs and NNRTIs. In cross-examination he acknowledged that he had searched for such papers, but not found any. Dr Spaltenstein did, however, exhibit a short review article by John Saunders, "Non-Nucleoside Inhibitors of HIV Reverse Transcriptase: Screening Successes – Clinical Failures", *Drug Design and Discovery*, 8(4), 255-263 (1992) ("Saunders"). The final section of Saunders discussed the rapid emergence of resistance to NNRTIs and concluded (at 262):

> "Current opinion therefore is that these agents are unsuitable for monotherapy and, at best, will only have a role to play in combination with nucleoside analogs. Given that there is increasing evidence[19] that such agents act synergistically to

> inhibit HIV replication in MT-4 cells whereas cytotoxic effects remain unchanged, this may still represent a modest addition to the limited repertoire of drugs available to combat AIDS."

130. Dr Spaltenstein exhibited Saunders as being reflective of the common general knowledge in August 1992. Prof Seley-Radtke did not take issue with that in her second report. Despite that, MSD raised an issue at trial as to when Saunders had been published. The best evidence as to its publication date is provided by a British Library catalogue entry which gives July 1992 as the date.

131. In her second report Prof Seley-Radtke disagreed that it was routine to consider combining a NRTI with a NNRTI in August 1992. She said that, in reviewing Schinazi, which Dr Spaltenstein had exhibited to his report, she had noticed a reference to an article by Masanori Baba *et al.*, "Synergistic Inhibition of Human Immunodeficiency Virus Type 1 Replication by 5-Ethyl-1-Ethoxymethyl-6-(Phenylthio)Uracil (E-EPU) and Azidothymidine In Vitro", *Antimicrobial Agents and Chemotherapy*, 35(7), 1430-1433 (July 1991). (This paper was also reference 19 in Saunders.) Prof Seley-Radtke explained that E-EPU was now understood to be a NNRTI, but said that in August 1992 a substantial proportion of skilled persons would have regarded it as a NRTI. She went on to say that, even if this paper was included, there were only two published studies showing *in vitro* results for a combination of a NRTI and a NNRTI in August 1992 (the other one being Richman).

132. Searches by the Claimants' representatives demonstrated, however, that that statement was inaccurate. At least one other paper and an abstract had been published by August 1992:

i) Mark Goldman *et al.*, "Pyridinone derivarives: Specific human immunodeficiency virus type 1 reverse transcriptase inhibitors with antiviral activity", *Proc. Natl. Acad. Sci. USA*, 88, 6863-6867 (August 1991) ("Goldman"). This reported synergism between combinations of AZT and ddI with the MSD compounds L697,639 and L-697,661, two pyridinone derivatives that are NNRTIs (the latter of which is referred to in the Patent).

ii) R.W. Buckheit Jr *et al.*, "Combinations of AZT and Analogs of TIBO Act Synergistically to Inhibit HIV-1 Infection In Vitro", *Antiviral Research*, 17 (Supplement 1) (March 1992). This reported synergism between AZT and two TIBO derivatives, but without any data.

133. In addition, there were a number of other papers which suggested combining NRTIs and NNRTIs, albeit that they did not report the results of testing such a combination:

i) Richard Koup *et al*, "Inhibition of Human Immunodeficiency Virus Type 1 replication by the dipyridodiazepinone BI-RG-587", *J. Inf. Dis.*, 163, 966-970 (May 1991) ("Koup"), which is reference 52 in Mazzulli and Hirsch. Koup reported inhibition of HIV-1 by nevirapine. It stated towards the end of the discussion section (at 969):

> "The description of RT inhibitors that act at sites separate from nucleoside analogues may help limit the toxicities of those

> agents [43] and allow for therapeutic strategies using combinations of RT inhibitors."

ii) Jack Nunberg *et al*., "Viral Resistance to Human Immunodeficiency Virus Type 1-Specific Pyridinone Reverse Transcriptase Inhibitors", *J. Vir.*, 65(9), 4887-4892 (September 1991) ("Nunberg"), which reported inhibition of HIV-1 by three pyridinone NNRTIs, one of which was stated to be in initial safety and tolerability studies in humans. Nunberg concluded with the following statement (at 4891):

> "Combination therapies comprising the use of HIV-1-specific RT inhibitors and nucleoside analog RT inhibitors, such as AZT and dideoxyinonsine, will play an important role in minimizing the likelihood that drug-resistant strains of HIV-1 emerge. These treatment approaches may also benefit from potential synergism between the antiviral effects of these mechanistically different inhibitors of RT (11, 30)."

Reference 11 was Goldman and reference 30 was Richman.

iii) Peter Grob *et al.*, "Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase: Nevirapine as a Prototype Drug", *AIDS Research and Human Retroviruses*, 8(2), 145-152 (February 1992) ("Grob"), which reported and reviewed studies on nevirapine. Grob noted that nevirapine had been found to be synergistic in combination with AZT, citing Richman. Grob concluded with the following statement (at 151):

> "… it may be expected that HIV-1 mutants may arise upon long-term exposure to these nonnucleoside RT inhibitors. The clinical ramifications of this will be the need for combination drug therapy where the appearance of virus resistant to both antiviral therapeutic agents will be minimized. The nonnucleoside inhibitors have already proved useful tools in understanding RT structure-function relationships. These compounds are currently undergoing clinical evaluation for their potential as the next generation of anti-AIDS therapeutics."

134. Counsel for MSD submitted that none of the papers referred to in paragraphs 132-133 above could be common general knowledge given that both experts had searched for relevant papers and had not found them. I acknowledge the force of that submission, although in the case of Koup it is slightly blunted by the fact that it was cited as a reference in a book chapter that both experts considered to be reflective of the common general knowledge. Counsel for the Claimants made it clear in her closing submissions, however, that she was not contending that any of those papers was in and of itself common general knowledge. Rather, she submitted that the papers supported Dr Spaltenstein's evidence that it was routine to combine NRTIs and NNRTIs.

135. Counsel for the Claimants also submitted that this had been "all but accepted" by Prof Seley-Radtke after being taken through these papers in cross-examination. I do not

agree with this. Prof Seley-Radtke maintained that it was not routine to combine NRTIs and NNRTIs. What Prof Seley-Radtke did accept, however, was that people were considering and trying combinations of NRTIs and NNRTIs.

136. The conclusion I draw from the evidence of the experts and the documentary evidence considered as a whole is that it was common general knowledge that combinations of NRTIs and NNRTIs were at least worth considering, because evidence was emerging that NNRTIs were unlikely to be efficacious in monotherapy, but it was appreciated that their different mechanism of action to NRTIs meant that there were potential advantages to combining the two.

137. The final issue is as to the extent to which the skilled person could predict the result of combining a NRTI with a NNRTI in an *in vitro* test from their common general knowledge. The Claimants contend that the skilled person could predict with reasonable confidence that the combination would be either synergistic or additive, whereas MSD disputes this. Dr Spaltenstein's evidence supported the Claimants' contention, whereas Prof Seley-Radtke's evidence was that the skilled person could not predict the outcome.

138. In addressing this issue it is important, as counsel for the Claimants submitted, to focus on the correct question. The issue is not whether the skilled person could predict what would happen *in vivo*. It is common ground that this was much more difficult to predict, even from *in vitro* results. Equally, the issue is not whether the skilled person could predict with reasonable confidence that the combination would be synergistic: although synergy was preferable, an additive effect might be useful.

139. Prof Seley-Radtke pointed out that there were limited data available for any combinations of HIV drugs in August 1992, which is undoubtedly correct. According to the available data, however, most of the combinations tested had been found to be synergistic, and only one had been found to be antagonistic. Moreover, as Prof Seley-Radtke accepted, the literature shows that some groups of workers were prompted to test combinations of NRTIs and NNRTIs by the prospect that they might be synergistic, namely the authors of Goldman (a team from MSD) and of Grob and Richman (a team from Boehringer Ingelheim).

140. The conclusion I draw from the evidence of the experts and the documentary evidence considered as a whole is that the skilled person would have considered that there was a reasonable likelihood that a combination of a NRTI and a NNRTI would be either synergistic or additive *in vitro*, and a reasonable possibility that it would be synergistic, although they would know that they had to test the combination to find out.

Construction of claim 16

141. There was no dispute as to the principles to be applied when construing patent claims. As noted above, there are two issues as to the construction of claim 16. Before turning to those, it is important to note two points which are not in issue. First, claim 16 does not require efficacy *in vivo*. Secondly, claim 16 does not require synergy.

"*Nucleoside analog*"

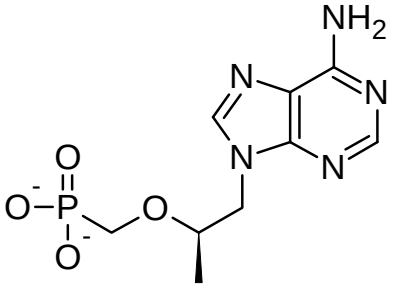
142. The first issue is whether tenofovir is a "nucleoside analog" within the meaning of claim 16. MSD contends that it is, whereas the Claimants contend that it is not. As counsel for MSD submitted, the correct approach to this question is first to construe the claim and then to determine whether, on that construction, tenofovir falls within it. For the reasons given above, the claim must be construed as at August 1992. It is immaterial that tenofovir was not known to have activity against HIV reverse transcriptase at that date.

143. It was common ground between the experts that, to a medicinal chemist, an "analogue" is a compound having a structure which is similar to that of another compound, but which differs in respect of a certain component. Accordingly, a nucleoside analogue is a nucleoside that has been structurally modified in some way. Furthermore, that definition was as applicable in 1992 as it is now.

144. Dr Spaltenstein was not able to point to anything in the Patent that suggested to the skilled reader that the patentee was using the term "analog" in claim 16 in anything other than the standard way.

145. As explained in paragraphs 47 above, a nucleoside consists of a five-carbon cyclic sugar and a base. As the experts agreed, when a phosphate group is attached to the molecule, the compound can be referred to either as a nucleotide or a nucleoside monophosphate. Dr Spaltenstein also agreed that adenosine monophosphate could be considered to be a nucleoside analogue because it was an analogue of the nucleoside, adenosine. Accordingly, MSD contends that the skilled person would understand that the term "nucleoside analog" in claim 16 encompassed nucleotides such as adenosine monophosphate. I agree with this.

146. Tenofovir consists of an adenine base linked to a three-carbon acylic sugar with a phosphonate (-CH_2-PO_3) group. Its structure is set out below.



147. The experts were agreed that tenofovir could properly be described as both a nucleoside analogue and a nucleotide analogue. Consistently with this, tenofovir is referred to in the literature, both before and after the priority date, by both names. In fact, even Erik de Clercq and Antonin Holý, who invented the acylic phosphonates such as tenofovir, used both names, both before and after the priority date.

148. A further point is that, although claim 16 requires the presence of a "nucleoside analog having biological activity against HIV reverse transcriptase", the skilled person would understand that a nucleoside analogue is not itself active against HIV reverse transcriptase. Before it can have that activity, it has to be converted into a

nucleotide (a nucleoside triphosphate) by the addition of three phosphate groups. Similarly, a nucleotide with a single phosphate (a nucleoside monophosphate) would not be active until it was converted into a triphosphate by the addition of two phosphates. The skilled person would therefore understand that, regardless of whether a particular agent was delivered as a nucleoside or a nucleotide, both are prodrugs of the same active agent (the triphosphate). Each would need to be converted into that same active agent and would then work in the same way to inhibit HIV reverse transcriptase, by being incorporated into the growing DNA chain and terminating it. Because of this, the skilled person would not understand that the patentee was intending to exclude nucleoside analogues that were also nucleotides or nucleotide analogues from the scope of the claim.

149. Consistently with this, Dr Spaltenstein accepted that probably the best definition of a NRTI was something that, once it was in the patient, was capable of being phosphorylated by kinases, so that it can compete with natural nucleosides and terminate a DNA chain once it has been incorporated. Tenofovir satisfies this functional definition in the same way as other NRTIs such as emtricitabine and AZT. Once it has had two phosphate groups added to its phosphonate group by kinase enzymes in the body, it is analogous to a nucleoside triphosphate. It inhibits HIV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, by being incorporated into the growing DNA strand, terminates it by stopping further growth. Thus the skilled person would understand that tenofovir functioned to inhibit HIV reverse transcriptase in the same way as other nucleoside analogues.

150. Dr Spaltenstein suggested that the skilled person would have considered that an acylic phosphonate would be too polar to cross the phospholipid membrane of a cell, but Prof Seley-Radtke did not agree with this and I prefer her evidence on this point. In any event, as Dr Spaltenstein accepted, it was standard practice in August 1992 to administer polar compounds in the form of a prodrug which is converted into the active agent in the body. This is in fact what happened with tenofovir: it is administered in the form of TDF, which is a prodrug, because tenofovir itself has poor oral bioavailability (although it could have been administered by another route). I would add that, as pointed out above, claim 16 does not require activity *in vivo*.

151. Accordingly, I conclude that tenofovir is a "nucleoside analog" within the meaning of claim 16.

"*A nucleoside analog*"

152. The Claimants contend that the skilled person would understand "a" to mean one and one only. MSD contends that the skilled person would understand "a" to mean at least one and thus as extending to more than one.

153. Counsel for the Claimants advanced the following arguments in support of the Claimants' construction. First, the word "a" is not a term of art, but an ordinary, English word used to denote the singular. The skilled reader would understand from this use of language that the patentee was intending to limit claim 16 (and claim 7) to double combinations.

154. Secondly, the skilled reader's understanding would be reinforced by the fact that the patentee uses the term "one or more" elsewhere in the claims (see claims 8 and 9) and in the specification (see [0046] quoted in paragraph 86 above). Thus the patentee's uses of the term "a" in certain claims, but the term "one or more" in other claims, would be understood as constituting a deliberate choice by the patentee.

155. Thirdly, the skilled reader would consider that the limitation in claim 16 accorded with the patentee's teaching in the specification that compounds of Formulae I and II (including efavirenz) may be combined with a (singular) nucleoside analogue having activity against reverse transcriptase (see [0047] quoted in paragraph 88 above).

156. Fourthly, the skilled reader would also note that the specification refers at [0053] (quoted in paragraph 90 above) both to double combinations and triple combinations, reinforcing the view that the patentee has adopted a deliberate and specific approach to the number of components of any particular combination.

157. Counsel for MSD advanced the following arguments in support of MSD's construction. First, the words of the claim did not say "one and only one". Accordingly, they were apt to cover a combination with one or more nucleoside analogues. In support of this submission, counsel relied upon EPO Board of Appeal decision T 405/00 *Unilever/Bleaching tablet* (unreported, 14 October 2004).

158. Secondly, as Dr Spaltenstein accepted, the Patent as a whole contemplated combinations of efavirenz with more than one nucleoside analogue.

159. Thirdly, the specification made it clear at [0045], [0046] and [0047] that part of the invention was combinations of Formulae I and II with one or more other agents.

160. Fourthly, claim 9 supported MSD's interpretation when read together with the specification at [0053].

161. In my judgment the Claimants' construction is the correct one for the reasons advanced by counsel for the Claimants. I do not accept the arguments advanced by counsel for MSD for the following reasons.

162. First, decision T 405/00 turned on the presence of the word "comprising" in the claim in question, whereas it does not appear in claim 16.

163. Secondly, the fact that the Patent as a whole contemplates combinations of efavirenz with more than one nucleoside analogue does not demonstrate that claim 16 should be construed as covering such combinations given that they are covered by claims 8 and 9.

164. Thirdly, the reference in [0045] to "nucleoside analogs" does not show that combinations of nucleoside analogues are contemplated. The reference in [0046] to "one or more agents useful in the treatment of AIDS" has to be read in context. As the following sentence makes clear, what the patentee is talking about at that point is combinations of a range of agents, not just antivirals but also immunomodulators and so on such as those listed in the table. By contrast, the specification states at [0047] that "a compound of Formula I or II" may be combined with "a nucleoside analog". This is evidently the basis for claim 7, of which claim 16 is a subset.

165. Fourthly, I agree with counsel for MSD that claims 8 and 9 correspond to preferred combinations (1) and (2) in [0053]. I do not accept his argument that the specific combinations of claims 8 and 9 are examples of, and therefore subsets of, the combinations described in the opening part of that paragraph, namely combinations with "a nucleoside". What the beginning of [0053] actually says is that preferred combinations are combinations of efavirenz with a PI (the words "or without" must be a mistake) and that "[a]n optional third component" is "a nucleoside inhibitor of HIV reverse transcriptase" such as AZT, ddC or ddI. It then says that another preferred reverse transcriptase inhibitor is L-697,661. It then says that preferred combinations include the ones corresponding to claims 8 and 9. Thus the reference to "a nucleoside inhibitor" is in the context of describing an "optional third component" for a combination of efavirenz and a PI. It is fair to say that preferred combination (1) extends to a combination of efavirenz, L-735,524 and more than one of L-697,661, AZT, ddI or ddC, but this is conveyed by the use of the words "any of" and confirmed by the words "one or more of" in claim 8. If more than one of those is present, then there are four components in the combination. In my view the skilled reader would not understand from this that "a nucleoside" meant "one or more" even in the context of [0053], let alone in the context of claim 16. I would add that this argument is exactly the sort of meticulous verbal analysis deprecated in the authorities.

The Claimants' case under Article 3(a)

166. For the reasons given above, I have concluded that the scope of protection of claim 16 of the Patent extends to a combination of efavirenz and tenofovir or to a combination of efavirenz and emtricitabine, but not to a combination of all three.

167. Since the minimum requirement for a product to be "protected" by a basic patent within the meaning of Article 3(a) of the SPC Regulation is that the product falls within the extent of protection of at least one claim, it follows that the Product is not "protected" by the Patent. Accordingly, the SPC is invalid because it does not comply with Article 3(a).

The Claimants' case under Article 3(c)

168. For the purposes of considering the Claimants' case under Article 3(c), I shall assume, contrary to the conclusion reached above, that claim 16 covers the combination of efavirenz with one or more nucleoside analogues active against reverse transcriptase, and hence covers the Product.

169. There is no dispute that the principal invention disclosed and claimed in the Patent is the class of compounds of which efavirenz is the most preferred example. By the end of the trial, it was common ground between counsel that, given that (i) efavirenz was protected by the Patent and (ii) MSD had already obtained the 035 SPC in respect of efavirenz, then Article 3(c) precluded the grant of the SPC in respect of the Product unless claim 16 of the Patent was independently valid over the claims which protected efavirenz and thus represented a distinct invention from the invention protected by those claims.

170. Counsel for the Claimants submitted that it should be assumed for this purpose that the skilled person had efavirenz and its activity against HIV reverse transcriptase disclosed to them at the priority date. Although counsel for MSD took issue with this,

I consider that it is correct. The question to be considered is not the conventional one of whether a claim is invalid over a particular item of prior art read in the light of the common general knowledge, but whether, given the invention of efavirenz, claim 16 represents a distinct invention such that it could in principle form the subject-matter of a separate patent.

171. Considered in that way, I consider that claim 16 is not independently valid over the claims which protect efavirenz and does not represent a distinct invention. There is nothing in the Patent to suggest that claim 16 represents a distinct invention. Given the need for a simple and transparent system for the grant of SPCs, it seems to me that that should ordinarily be the end of the matter and that it should not be necessary to adduce expert evidence on this question.

172. If it is appropriate to have regard to the expert evidence, however, I consider that the evidence establishes that, given efavirenz, it would have been obvious to combine it with a NRTI *in vitro* because that would have been an obvious thing to try and the skilled person would have had a fair expectation of success. This is for the following combination of reasons.

173. First, the skilled person had a very strong motivation to find new treatments for HIV (see paragraph 77 above).

174. Secondly, the idea of combination therapy was accepted as a basis for further action and interest in combinations of HIV drugs was growing (see paragraph 77 above).

175. Thirdly, it was common general knowledge that combinations of NRTIs had demonstrated synergy *in vitro* and were undergoing clinical trials. Moreover, the rationale for combining NRTIs was not peculiar to that class of antivirals (see paragraphs 116-119 above).

176. Fourthly, it was common general knowledge that combinations of NRTIs and NNRTIs were at least worth considering, because evidence was emerging that NNRTIs were unlikely to be efficacious in monotherapy, but it was appreciated that their different mechanism of action to NRTIs meant that there were potential advantages to combining the two (see paragraph 136 above)

177. Fifthly, as discussed above, at least two groups had published studies of combinations of NRTIs and NNRTIs by the priority date (see paragraph 139 above). There is nothing to suggest that those workers considered that combining NRTIs and NNRTIs was inventive. Still less would it have been inventive a year after the publication of Goldman and 18 months after the publication of Richman.

178. Sixthly, the skilled person would have considered that there was a reasonable likelihood that a combination of a NRTI and a NNRTI would be either synergistic or additive (see paragraph 140 above).

179. Seventhly, as Dr Spaltenstein explained, testing a combination of a NRTI and a NNRTI for reverse transcriptase inhibitory activity *in vitro* was not a difficult or labour-intensive experiment to carry out.

180. Eighthly, I do not accept the submission advanced by counsel for MSD that the skilled person would be deterred by the fact that, by August 1992, it was known that NNRTIs were failing as monotherapies due to the rapid emergence of resistance. It can be seen from the literature that, in general, resistance to single agents was one of the reasons for trying combination therapy. Furthermore, papers such as Nunberg, Grob and Saunders show that the same thinking was applied to combinations of NRTIs and NNRTIs.

181. Finally, it was Prof Seley-Radtke's evidence that the data in Table S of the Patent did not enable the skilled person to predict that a combination of efavirenz and a NRTI other than the combinations for which data was reported would be synergistic or additive. It follows that, in that respect, the Patent did not advance scientific knowledge beyond papers such as Goldman, as I think Prof Seley-Radtke accepted.

Conclusion

182. I conclude that the SPC is invalid because it does not comply with either Article 3(a) or Article 3(c) of the SPC Regulation.