Intellectual Property Office

BL O/117/16

12 January 2016

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

APPLICANT	Merck Sharp & Dohme Corporation.
ISSUE	Whether application SPC/GB14/062 for a supplementary protection certificate meets the requirements of Article 3(b) and Article 3(c) of the Regulation
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 This decision relates to an application for a supplementary protection certificate (SPC) which was filed by Merck Sharp & Dohme ("the applicant") on 12th September 2014 and was accorded the number SPC/GB14/062.

2 This SPC application concerns the product "*Ezetimibe and atorvastatin or pharmaceutically acceptable salts thereof, including atorvastatin as atorvastatin calcium trihydrate*" (see section 6 of form SP1). Ezetimibe and atorvastatin is the combination of active ingredients present in the medicinal product, ATOZET (RTM[1]).

3 The basic patent on which this SPC application relies is EP (UK) 0720599 B1, entitled "*Hydroxy-substituted Azetidinone Compounds Useful as Hypocholesterolemic Agents*". It was filed on 14th September 1994 with an earliest priority date of 21 September 1993. The basic patent expired on 13th September 2014, a day after the filing of the SPC application.

4 The applicant did not provide any details of a Marketing Authorisation (MA) in support of their SPC application (see sections 8 and 9 of Form SP1 filed with this application). Instead the applicant made reference to a document referred to as the End of Procedure Communication of Approval, dated 10 September 2014, for procedure DE/H/3895-3898/001-004/DC. A copy of this communication, an email from the *Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)* [the German

[1] The glossary at the end of this decision provides an explanation of this and the other abbreviations used throughout the decision.

Medicines Agency][2] was provided with form SP1. This email is entitled "*FW: DE/H/3895-3898/01-04/DC Atozet et al- D209 End of Procedure documents*" and by way of explanation of this document, the applicant stated the following in the cover letter, dated 11 September 2015, sent with their application and Form SP1:

> *"The End of Procedure communication of approval and enclosures for ATOZET (active ingredients: ezetimibe and atorvastatin calcium trihydrate) from the German Medicines Agency (the RMS) are enclosed with this application. The End of Procedure communication closes the Decentralised approval procedure, which confirms that all the concerned member states (the CMSs) are in agreement with the RMS and agree to grant marketing authorisations for this product.*
>
> *Each member state including the UK will now carry out the formal step of granting the national marketing authorisation."*

5 As a result, the applicant requested that he *"be able to supplement this SPC application with the marketing authorization for the UK, and, if this is not the first authorisation in the Community, additionally with that marketing authorisation".*

6 I note that in addition to the SPC application at issue in the present case, there are two earlier granted SPCs in the UK which rely on the same basic patent:

(i) SPC/GB03/023 for the product '*Ezetimibe and pharmaceutically acceptable salts thereof*' which was granted on 23 October 2003 and entered into force when the patent expired on 14 September 2014 and will itself expire on 16 October 2017; and

(ii) SPC/GB05/010 for the product '*Ezetimibe or a pharmaceutically acceptable salt thereof in combination with simvastatin*' which was granted on 30 June 2005 and entered into force when the patent expired on 14 September 2014. This SPC will itself expire on 1 April 2019.

7 Given the proximity to the patent expiry date, the examiner wrote promptly to the Applicant, and in his first official report, dated 17 September 2014, raised two objections – the first objection that the application did not comply with Article 3(b) because he considered that the application did not comprise a valid MA in the UK. The *End of Procedure Communication of Approval* did not meet this requirement as the MA had not yet been granted in the UK.

8 The second objection raised by the examiner concerned compliance with Article 3(c) wherein the examiner, applying the decision of the CJEU in *Actavis Group PTC EHF and Actavis UK Limited v Sanofi and Sanofi Pharma Bristol-Myers Squibb SNC,* C-433/12, hereafter "*Sanofi*"[3], to the facts of this application, argued that, given that an SPC for the active ingredient – ezetimibe – had already been granted, an application for an SPC comprising this active ingredient in combination with atorvastatin, would provide additional protection for ezetimibe, and, as such, was not allowed under

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[2] See http://www.bfarm.de/EN/Home/home_node.html.

[3] Reference for a preliminary ruling from United Kingdom, High Court of Justice (England & Wales), Chancery Division, made by decision of that court of 21 September 2012, received at the CJEU on 3 October 2012.

Article 3(c) of the Regulation as this active ingredient had already been the subject of a certificate

9 The examiner and the Agent entered into several additional rounds of correspondence. The agent responded to the first official report on 17 November 2014. The examiner sent a second official report dated 27 November 2014. The agent responded to the second official report on 27 February 2015. The examiner sent a third official report on 11 March 2015. In the latter report, the examiner set out the issues as he saw them that remained to be decided and, given that these matters had been the subject of a number of rounds of correspondence but had still not been resolved, he suggested the Applicant consider requesting a hearing. An oral hearing was agreed and arranged for 3 September 2015.

10 In advance of the hearing, on 7 August 2015, the Office wrote to the Agent on behalf of Hearing Officer and asked the Applicant to address a number of questions in their submissions before or at the hearing. These included addressing the relevance of the judgment by the CJEU in *Actavis Group PTC EHF and Actavis UK v Boehringer Ingelheim Pharma*, C-577/13, hereafter "*Boehringer*"[4]. This judgment was issued on 12 March 2015. The Applicant filed a skeleton argument on 26 August 2015 with associated witness statements and exhibits, one week in advance of the hearing. This material was very helpful and I would like to record my thanks to the applicant for providing this material in advance of the hearing.

11 This SPC application came before me at an oral hearing held at the Intellectual Property Office in Newport on 3 September 2015. In attendance at the hearing were the agent representing the Applicant, Mr James Horgan (Chartered Patent Attorney, Merck Sharp & Dohme), his assistant, Deeba Hussain (Chartered Patent Attorney, Merck Sharp & Dohme) and Stephen Bennett (Solicitor, Hogans Lovell LLP). The examiner, Mr Jason Bellia, also attended. Two observers were also present.

The Basic Patent

12 The basic patent EP (UK) 0720599 B1, filed in support of this application, comprises, as its main claim 1, a Markush formula. It is not in dispute that this Markush formula encompasses Ezetimibe. In relation to compositions which comprise more than one pharmaceutically active compound, I note the scope of dependent claims 9, 16 and 17 as follows:

> *"9.* ***A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound as claimed in any one of the claims 1 to 8****, alone or* ***in combination with a cholesterol biosynthesis inhibitor, in a pharmaceutically acceptable carrier****.*
>
> *...*
>
> *16. A pharmaceutical composition of any of claims 9, 12 or 15 wherein the cholesterol biosynthesis inhibitor is selected from the group*

[4] Reference for a preliminary ruling from United Kingdom, High Court of Justice (England & Wales), Chancery Division (Patents Court) (United Kingdom), made by decision of 31 October 2013, received at the Court on 14 November 2013.

*consisting of **HMG CoA reductase inhibitors**, squalene synthesis inhibitors and squalene epoxidase inhibitors.*

*17. A pharmaceutical composition of claim 16 wherein the cholesterol biosynthesis inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvastatin, simvastatin, **CI-981**, DMP-565, L659,699, squalestatin 1 and NB-598."*

It is a matter of public record, and it has also has been confirmed by the examiner, that CI-981 is an alternative name for atorvastatin[5].

Issues to be decided

13 There are 2 issues to be decided in respect of the present SPC application:

(i) Does the application comply with Article 3(b)? i.e. was this application on the date it was made the subject of '*a valid authorisation to place the product on the market as a medicinal product granted in accordance with Directive 2001/83*/EC';

and

(ii) Does the application comply with Article 3(c)? i.e., is the active ingredient for which the SPC is sought already the subject of an earlier granted certificate. In this regard and, as noted already, it is not in dispute that (the Markush formula in) claim 1 encompasses the active ingredient Ezetimibe. What is at issue is whether the application provides the basis for the combination of ezetimibe with atorvastatin?

14 Failure to meet either of the above requirements under Article 3 will result in the refusal of the SPC application under Article 10(2).

The Role of the IPO is to grant SPCs

15 It is appropriate at this point to observe that the Intellectual Property Office (IPO) is the body responsible for granting SPCs in the UK (see Article 9 of the SPC Regulation and Section 128B of the Patents Act 1977) and, in this role, it is necessary to determine if the applications received meet the requirements of the SPC regulation, in particular, Article 3. If an application for an SPC does meet these requirements, an SPC shall be granted (see Article 10 of the SPC Regulation). The SPC is granted for a period of time, calculated using the algorithm outlined in Article 13, for a product that is covered by a patent, referred to as the basic patent, and is the active ingredient (or combination of active ingredients) in a medicinal product which has been authorised for human use under Directive 2001/83/EC. The SPC provides the applicant with an additional period of exclusivity after the patent expires to balance the loss of patent term they have experienced while gaining the necessary regulatory approval, i.e. the marketing authorisation, to place the

[5] See entry for ***atorvastatin*** at https://en.wikipedia.org/wiki/Atorvastatin

medicinal product comprising this active ingredient (or combination of active ingredients) on the market for human use.

16 The IPO is concerned with the process for the grant of the SPC and not the process for the grant of the marketing authorisation for the medicinal product. The latter is the responsibility of the Medicines and Healthcare Products Regulatory Agency (MHRA) at the national level in the UK[6], and of the European Medicines Agency (EMA) at the European Community wide level[7]. However, in order to address whether Article 3(b) of the SPC Regulation has been satisfied, it is necessary to consider the legislation and the process involved in the grant of the marketing authorisation. The IPO considers the process for the grant of marketing authorisations in so far as it is necessary to establish if a valid marketing authorisation has been granted for the purpose of fulfilling the requirements of Article 3(b) of the SPC regulation.

17 In this particular case, the Hearing Officer at the IPO has had to consider how the decentralised procedure works in order to determine when exactly the marketing authorisation is granted under this procedure.

18 The analysis presented below is based on my consideration of Directive 2001/83/EC and the related guidance on the decentralised procedure, the relevance of the cited CJEU decisions as well as my consideration of all the material provided by the applicant in the skeleton argument and at the oral hearing and the material on file in terms of the correspondence between the examiner and the applicant.

Does the Application Comply With Article 3(b)?

The Relevant Law

19 It is a common tenet of EU law that it is defined having regard to both the purpose of the relevant EU legislation - as set out in the recitals - and the articles which provide the substance of the law. In this instance, we are concerned with the SPC regulation[7] and the Medicinal Products Directive[8]. I reproduce the relevant parts of this legislation below (with my emphasis added in **bold**).

The SPC Regulation – Regulation EC 469/2009[8]

20 Recitals 2-5, 7, 9 and 10 of the SPC Regulation state (emphasis added):

> *'(2) Pharmaceutical research plays a decisive role in the continuing improvement in public health.*

[6] See MHRA website at http://www.mhra.gov.uk/index.htm#page=DynamicListMedicines
[7] See EMA website at http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=
[8] Regulation (EC) 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products.

(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.

…

(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 functioning of the internal market.

...

(9) The duration of the protection granted by the certificate should be such as to provide adequate effective protection. For this purpose, the holder of both a patent and a certificate should be able to enjoy an overall maximum of 15 years of exclusivity ***from the time the medicinal product in question first obtains authorisation to be placed on the market in the Community****.*

(10) ***All the interests at stake, including those of public health, in a sector as complex and sensitive as the pharmaceutical sector should nevertheless be taken into account****. For this purpose, the certificate cannot be granted for a period exceeding five years.* ***The protection granted should furthermore be strictly confined to the product which obtained authorisation to be placed on the market as a medicinal product****.'*

21 Article 1 of the SPC Regulation provides the definition of 'product ' and 'medicinal product' as follows:

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

(a) 'medicinal product' means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;

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

.....

22 Article 2 of the SPC Regulation defines the scope of the regulation (emphasis added) and reads:

Any product protected by a patent in the territory of a Member State and subject, prior to being placed on the market as a medicinal product, to an administrative authorisation procedure as laid down in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use *or Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products* ***may, under the terms and conditions provided for in this Regulation, be the subject of a certificate****.*

23 Article 3 of the Regulation defines the conditions for obtaining a certificate (emphasis added) reads as follows:

> *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 if that application:*
> *(a) ...*
>
> ***(b) a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC or Directive 2001/82/EC, as appropriate;***
>
> *(c) ....*
>
> *(d) ...*

24 Article 7, entitled 'Application for a certificate', sets out the deadlines and time periods for making an application for an SPC and it reads as follows:

> *"1. The* ***application for a certificate*** *shall be lodged within six months of the date on which the authorisation referred to in Article 3(b) to place the product on the market as a medicinal product was granted.*
>
> *2. Notwithstanding paragraph 1, where the authorisation to place the product on the market is granted before the basic patent is granted,* ***the application for a certificate*** *shall be lodged within six months of the date on which the patent is granted.*
>
> *3. The* ***application for an extension of the duration*** *may be made when lodging the application for a certificate or when the application for the certificate is pending and the appropriate requirements of Article 8(1)(d) or Article 8(2), respectively, are fulfilled.*
>
> *4. The* ***application for an extension of the duration*** *of a certificate already granted shall be lodged not later than two years before the expiry of the certificate.*
>
> *5. Notwithstanding paragraph 4, for five years following the entry into force of Regulation (EC) No 1901/2006, the application for an extension of the duration of a certificate already granted shall be lodged not later than six months before the expiry of the certificate*."

25 Article 8 of the SPC Regulation which concerns the content of an application for an SPC reads as follows (emphasis added):

> ***Content of the application for a certificate***
>
> *1. The application for a certificate shall contain:*

(a) a request for the grant of a certificate, stating in particular:

(i) the name and address of the applicant;

(ii) if he has appointed a representative, the name and address of the representative;

(iii) the number of the basic patent and the title of the invention;

(iv) the number and date of the first authorisation to place the product on the market, as referred to in Article 3(b) and, if this authorisation is not the first authorisation for placing the product on the market in the Community, the number and date of that authorisation;

(b) a copy of the authorisation to place the product on the market, as referred to in Article 3(b), in which the product is identified, containing in particular the number and date of the authorisation and the summary of the product characteristics listed in Article 11 of Directive 2001/83/EC or Article 14 of Directive 2001/82/EC;

(c) if the authorisation referred to in point (b) is not the first authorisation for placing the product on the market as a medicinal product in the Community, information regarding the identity of the product thus authorised and the legal provision under which the authorisation procedure took place, together with a copy of the notice publishing the authorisation in the appropriate official publication;

(d) where the application for a certificate includes a request for an extension of the duration:

(i) a copy of the statement indicating compliance with an agreed completed paediatric investigation plan as referred to in Article 36(1) of Regulation (EC) No 1901/2006;

(ii) where necessary, in addition to the copy of the authorisation to place the product on the market as referred to in point (b), proof of possession of authorisations to place the product on the market of all other Member States, as referred to in Article 36(3) of Regulation (EC) No 1901/2006. 2. Where an application for a certificate is pending, an application for an extended duration in accordance with Article 7(3) shall include the particulars referred to in paragraph 1(d) of this Article and a reference to the application for a certificate already filed. 3. The application for an extension of the duration of a certificate already granted shall contain the particulars referred to in paragraph 1(d) and a copy of the certificate already granted. 4. Member States may provide that a fee is to be payable upon application for a certificate and upon

2. Where an application for a certificate is pending, an application for an extended duration in accordance with Article 7(3) shall include the particulars referred to in paragraph 1(d) of this Article and a reference to the application for a certificate already filed.

3. The application for an extension of the duration of a certificate already granted shall contain the particulars referred to in paragraph 1(d) and a copy of the certificate already granted.

4. Member States may provide that a fee is to be payable upon application for a certificate and upon application for the extension of the duration of a certificate.

26 Article 10 entitled 'Grant of the certificate or rejection of the application for a certificate' sets out what happens if an application does not meet the requirements of the regulation and reads as follows:

"1. Where the application for a certificate and the product to which it relates meet the conditions laid down in this Regulation, the authority referred to in Article 9(1) shall grant the certificate.

2. The authority referred to in Article 9(1) shall, subject to paragraph 3, reject the application for a certificate if the application or the product to which it relates does not meet the conditions laid down in this Regulation.

3. Where the application for a certificate does not meet the conditions laid down in Article 8, the authority referred to in Article 9(1) shall ask the applicant to rectify the irregularity, or to settle the fee, within a stated time.

4. If the irregularity is not rectified or the fee is not settled under paragraph 3 within the stated time, the authority shall reject the application.

5. Member States may provide that the authority referred to in Article 9(1) is to grant certificates without verifying that the conditions laid down in Article 3(c) and (d) are met."

Directive 2001/83/EC - The Medicinal Products Directive[9]

27 No medicinal product may be placed on the market of a Member State (MS) unless an authorisation has been issued by the **national competent authority** (NCA) of that MS or by the EMA which provides a centralised authorisation procedure for medicinal products that covers the whole of the territory of the European Community. Only applicants established in the Community may be granted such a centralised marketing authorisation.

28 The European system offers three routes for the authorisation of medicinal products, (i) the so-called **centralized procedure,** using the EMA, which was mentioned already (set up in May 2004 by Regulation (EC) No 726/2004); and two procedures based on the principle of mutual recognition of national authorisation procedures; i.e., (ii) the **decentralised procedure** (DCP), and (iii) the **mutual recognition procedure** (MRP)[9]. Each MS has a **national competent authority** responsible for the granting of marketing authorisations for medicinal products in that territory. In

[9] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to Medicinal Products For Human Use – see http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&qid=1451584997171&from=EN.

UK, the NCA is the Medicines and Healthcare products Regulatory Agency (MHRA)[10].

29 The **decentralised procedure** (DCP) was introduced in 2004, and is used for medicinal products which have not yet been authorised in any EU member state and allows for the marketing authorisation application to be submitted simultaneously in several member states. The applicant arranges to use the NCA in one of these MS as the lead contact for both the applicant and for all the other competent bodies in the other member states. This lead contact NCA is referred to as the **Reference Member State** (RMS) and they coordinate the process for approval of the marketing authorisation application by mutual recognition so that at the end of the procedure national marketing authorisations are granted in all EU-MS involved.

30 If the medicinal product has already been granted a MA in one of the EU-MS, then the **mutual recognition procedure** (MRP), is used. This procedure is also based on the principle of recognition by one or more MS of an already existing national marketing authorisation from another MS.

31 Articles 28 to 39 make up Chapter 4 of the Directive, entitled '*Mutual recognition and decentralised procedure*, which, in turn, is part of Title III of the Directive, entitled '*Placing on the market*'. These eleven articles in Chapter 4 set out the basic steps necessary to implement both procedures based on mutual recognition of national marketing authorisations - DCP and MRP[11].

32 Not all types of medicinal products can be licensed using the decentralised procedure – Regulation (EC) 726/2004 makes clear that certain classes of medicinal product have to be licensed centrally through the EMA using the **centralized procedure**[12]. Furthermore, if the medicinal product is not one that needs to be licensed centrally, then the choice of whether to use the MRP or DCP is determined by whether or not an authorisation already exists for the medicinal product in one member state – if it does the MRP is used, if not the DCP is used (see Article 28(2) and Article 28(3) of the Directive).

33 In this case, we are concerned with an application under the **decentralised procedure** (DCP) for a marketing authorisation for a medicinal product that has not been authorised already in an EU member state.

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[10] See MHRA website on GOV.UK website at https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

[11] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the community code relating to medicinal products for human use; this directive added the details of the **decentralised** and **mutual recognition procedures** to Directive 2001/83/EC – see http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0027&rid=1

[12] Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency – see http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1451584721189&uri=CELEX:32004R0726. (The EU uses the US English spelling i.e. *centralized* in contrast to the UK English spelling – *centralised*)

Decentralised Procedure (DCP)

34 As noted above, the applicant chooses the national competent authority (NCA) of any member state to act as the RMS for the DCP. This NCA then acts as the contact point for all issues concerning the procedure for authorisation of this product both with the applicant and with all the competent bodies from the other member states [referred to as **concerned members states** (CMS)]. Each national competent authority (NCA) from a CMS will engage with the national competent authority of the RMS to raise any issues or matters that need attention and the RMS in turn will raise these issues with the applicant. Hereafter, a reference to the RMS means a reference to the NCA of the reference member state. The timetable for this process is laid down in Articles 28-39 of the Directive. For the purposes of this decision, Article 28, especially Article 28(5), is relevant.

35 The RMS selected by the applicant to coordinate the DCP for ATOZET is the national competent authority of Germany, the *Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)*[1]*.* The MHRA is involved in the process on behalf of the UK as one of the CMS.

Directive 2001/83/EC – relevant recitals and Articles

36 For the purposes of this case, the recitals and articles from Directive 2001/83/EC listed below are relevant.

37 Recital (2) refers to the essential aim of the Directive as follows:

> *"(2) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health."*

38 Recitals (7), (8), (11)-(15) and (37) refer to the importance of member states working together to license medicinal products for human use that provide the appropriate balance between risk and therapeutic effectiveness in a manner that uses the principles of mutual recognition to avoid unnecessary duplication of effort; i.e.:

> *(7) The concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.*
>
> *(8) Standards and protocols for the performance of tests and trials on medicinal products are an effective means of control of these products and hence of protecting public health and can facilitate the movement of these products by laying down uniform rules applicable to tests and trials, the compilation of dossiers and the examination of applications.*
>
> .....
>
> *(11) The adoption of the same standards and protocols by all the Member States will enable the competent authorities to arrive at their decisions on the basis of*

uniform tests and by reference to uniform criteria and will therefore help to avoid differences in evaluation.

(12) With the exception of those medicinal products which are subject to the centralized Community authorization procedure established by Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (1) ***a marketing authorization for a medicinal product granted by a competent authority in one Member State ought to be recognized by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health****. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to a Community standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.*

(13) For this purpose, a Committee for Proprietary Medicinal Products should be set up attached to the European Agency for the Evaluation of Medicinal Products established in the abovementioned Regulation (EEC) No 2309/93.

(14) This Directive represents an important step towards achievement of the objective of the free movement of medicinal products. Further measures may abolish any remaining barriers to the free movement of proprietary medicinal products will be necessary in the light of experience gained, particularly in the abovementioned Committee for Proprietary Medicinal Products.

(15) In order better to protect public health and avoid any unnecessary duplication of effort during the examination of application for a marketing authorization for medicinal products, Member States should systematically prepare assessment reports in respect of each medicinal product which is authorized by them, and exchange the reports upon request. Furthermore, a Member State should be able to suspend the examination of an application for authorization to place a medicinal product on the market which is currently under active consideration in another Member State with a view to recognizing the decision reached by the latter Member State.

.....

.....

(37) Authorization must be subject to certain essential conditions and it is the responsibility of the Member State concerned to ensure that such conditions are met; whereas each Member State must recognize authorizations granted by other Member States.

39 Article 6(1) of the Directive states as follows:

1. No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that

Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use (2) and Regulation (EC) No 1394/2007.

When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).

....

Article 6 is the first article found in Chapter 1, entitled '*Marketing authorization',* of Title III of the Directive entitled '*Placing on the market*'.

40 Article 8, in particular, Article 8(3)(i), of the Directive refers to the particulars and documents that need to be submitted with an application for a marketing authorisation. It refers to the submission of these documents and particulars in accordance with Annex 1 of the directive which describes the analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products. Articles 10, 10a, 10b, and 10c describe certain situations where the complete dossier of particulars and documents outlined in Article 8 are not required when making an application for a marketing authorisation. These situations are:

(i) where the medicinal product is a generic of a reference medicinal product which has already been authorised for at least 8 years (see Article 10),

(ii) where the active substance in the medicinal product has already been in active use in the community for at least 10 years (see Article 10a);

(iii) where medicinal product contains a combination of active substances which have already been used in authorised medicinal products but have not yet been used in combination only material relevant to the combination is required and not to the individual substances (see Article 10b);

(iv) where the marketing authorisation holder consents to the use of the documentation submitted as parts of its approval for the examination of subsequent applications relating to other medicinal products comprising the same active substances (see Article 10c).

For the purposes of the present case, the situation referred to in Articles 10b applied as this application related to a combination of two active ingredients, ezetimibe and atorvastatin, which had already been authorised as individual active ingredients in monotherapies and so the present application related to how these ingredients interacted in a combination.

41 Article 11 describes the information that must be provided in the Summary of Product Characteristics (SmPC) of the Marketing Authorisation.

42 Article 17 states as follows:

> ***1. Member States shall take all appropriate measures to ensure that the procedure for granting a marketing authorisation for medicinal products is completed within a maximum of 210 days after the submission of a valid application.***
>
> ***Applications for marketing authorisations in two or more Member States in respect of the same medicinal product shall be submitted in accordance with Articles 28 to 39.***
>
> ***2. Where a Member State notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, the Member State concerned shall decline to assess the application and shall advise the applicant that Articles 28 to 39 apply.***

Article 17 is the first article found in Chapter 3, entitled '*Procedures relevant to the marketing authorization*', of Title III of the Directive entitled '*Placing on the market*'.

43 As noted already, Article 28 and the following Articles 29-39 in Chapter 4 set down the mutual recognition and the decentralised procedure for marketing authorisations by national competent authorities (NCAs). For the purposes of this decision, Article 28, especially Article 28(5) is relevant. Article 28 of the directive states as follows (my emphasis added in bold):

> *"**1. With a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States. The dossier shall contain the information and documents referred to in Articles 8, 10, 10a, 10b, 10c and 11. The documents submitted shall include a list of Member States concerned by the application.***
>
> ***The applicant shall request one Member State to act as 'reference Member State' and to prepare an assessment report on the medicinal product in accordance with paragraphs 2 or 3.***
>
> *2. .....*
>
> *3. **In cases where the medicinal product has not received a marketing authorisation at the time of application, the applicant shall request the reference Member State to prepare a draft assessment report, a draft summary of product characteristics and a draft of the labelling and package leaflet. The reference Member State shall prepare these draft documents within 120 days after receipt of a valid application and shall send them to the concerned Member States and to the applicant.***
>
> *4. **Within 90 days of receipt of the documents referred to in paragraph**s 2 and **3**, **the Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and package***

leaflet and shall inform the reference Member State accordingly. The reference Member State shall record the agreement of all parties, close the procedure and inform the applicant accordingly.

5. ***Each Member State in which an application has been submitted in accordance with paragraph 1 shall adopt a decision in conformity with the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved, within 30 days after acknowledgement of the agreement.***

The Rules governing Medicinal Products in the European Union

44 The complete body of European Union (EU) legislation in the pharmaceutical sector is compiled in a publication referred to as "*The Rules governing Medicinal Products in the European Union*"[13]. Legislation and related guidelines in this area have been growing since the first EU directive on medicinal products in 1965 following the thalidomide affair[14]. The publication is divided into a series of 10 volumes and includes not only the texts of all the relevant legislation on medicinal products for human use (in Volume 1) but also includes all the various guidelines that have been produced to support this legislation and to help users navigate the different requirements and understand what is required for a successful marketing authorisation. The guidelines are of a regulatory, scientific and advisory nature. They are adopted as a means to facilitate the interpretation of the legislation and its uniform application across the EU. ***Table 1*** below summarises the different volumes in this publication which is available from the EudraLex website[13]. In this case, we are concerned with Volumes 1 and Volume 2. A detailed explanation of the marketing authorisation procedures and other regulatory guidance intended for applicants is contained in Volume 2 which is usually referred to as '*The Notice to Applicants*'[15]. The Notice to Applicants was first published in 1986 and is regularly updated to take account of changes in legislation and guidelines. It contains a list of regulatory guidelines related to the procedural and regulatory requirements for marketing authorisations for medicinal products for human use. For example, it includes guidelines relating to MA renewal procedures, preparation of SmPC, package labeling & readability requirements, product information leaflet requirements.

45 This Notice to Applicants has been prepared in accordance with Annex I of the Directive (and Article 6 of Regulation 726/2004) and is relevant to <u>all</u> marketing authorisations for medicinal products for human use; i.e. those obtained via the centralised route as well as those obtained via the procedures based on the principle of mutual recognition of national authorisation procedures. References throughout the Notice to Applicants to provisions of Directive 2001/83/EC (and Regulation (EC) 726/2004) must be read as references to the directive (and the regulation) as last amended, unless expressly stated otherwise. The legal provisions covering the mutual recognition procedure and the decentralised procedure for human medicinal products are contained in Directive 2001/83/EC.

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[13] All this material is available from the EU EudraLex website - see http://ec.europa.eu/health/documents/eudralex/index_en.htm.

[14] See http://www.sciencemuseum.org.uk/broughttolife/themes/controversies/thalidomide.aspx and footnote 9 above

[15] See EudraLex – Volume 2 at http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

Table 1: The volumes of "*The rules governing medicinal products in the European Union*" and the topics that each volume covers (volumes of interest are shaded/highlighted in yellow)

Volume	Topic covered	Contents
1	All EU Pharmaceutical legislation concerning medicinal products for **human** use	Directives, regulations and decisions
2	Notice to applicants and regulatory guidelines for medicinal products for **human** use	guidelines
3	Scientific guidelines for medicinal products for **human** use	guidelines
4	Guidelines for good manufacturing practices for medicinal products for **human** and veterinary use	guidelines
5	All EU Pharmaceutical legislation concerning medicinal products for veterinary use	Directives, regulations and decisions
6	Notice to applicants and regulatory guidelines for medicinal products for veterinary use	guidelines
7	Scientific guidelines for medicinal products for veterinary use	guidelines
8	Maximum residue limits	
9	Guidelines for pharmacovigilance for medicinal products for **human** and veterinary use	guidelines
10	Guidelines for clinical trials	guidelines

46 The Notice to Applicants has been prepared by the European Commission, in consultation with the competent authorities of each Member State and the EMA and is intended to facilitate the interpretation and application of the EU pharmaceutical legislation. The Notice to Applicants has no legal force and so is not legally binding. In case of doubt, reference should be made to the appropriate EU Directives and Regulations. However, the Notice to Applicants represents the harmonised view of the Member States, the EMA and the Commission services on how the legal requirements of the EU pharmaceutical legislation requirements may be met. For this reason, the Notice to Applicants provides the best available view on what the legal requirements of the EU pharmaceutical legislation requirements mean and how best to fulfil them.

47 Volume 2: the Notice to Applicants of "*The Rules governing Medicinal Products in the European Union*" is itself divided into a number of volumes[17] as follows:

(i) Volume 2A - Procedures for marketing authorisation
(ii) Volume 2B - Presentation and content of the dossier
(iii) Volume 2C - Regulatory Guidelines

Of interest in the present case is Volume 2A. Each of these volumes in the Notice to Applicants is, in turn, divided into a number of chapters. Volume 2A is divided into 7 chapters: Chapter 1 of Volume 2A is entitled "*Marketing Authorisation*" and it describes the general principles of the EU pharmaceutical legislation concerning

marketing authorisation of medicinal products for human use[15]. This is then expanded in greater detail in the following Chapters 2-7 which cover the different procedures for obtaining a marketing authorisation. Of interest in the presence case is Chapter 2 of Volume 2A which is entitled "*Mutual Recognition*"[16]. The most recent update for Chapter 1 was July 2015 whereas that for Chapter 2 was February 2007[15,16].

Mutual Recognition

48 Both the mutual recognition procedure (MRP) and the decentralised procedure (DCP) facilitate access to a single market, an important EU goal, by relying upon the principle of **mutual recognition**. Thus with the exception of those medicinal products which are subject to the centralised procedure (see Chapter 4 of Volume 2A of the Notice to Applicants), a granted marketing authorisation in one Member State (RMS) is recognised by the competent authorities in each of the other Member States (CMS), unless there are grounds for supposing that the authorisation of the medicinal product concerned may present a potential serious risk to public health. In the latter case, the CMS has to justify fully these grounds and the serious risk to public health has to be investigated and dealt with before the product can be authorised.

49 The NCAs who deliver marketing authorisations through the MRP and DCP work in conjunction with each other to share best practice. The **Heads of Medicines Agencies** (HMA) is a network of the heads of the national competent authorities (NCA) whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area[17]. The HMA co-operates with the EMA and the European Commission in the operation of the regulatory system for medicines in Europe.

50 The HMA have created a coordinating group, entitled the '*Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human',* or CMDh[18], which has produced a range of guidance on the authorisation procedures for medicinal products for human use based on the mutual recognition principle. This guidance includes best practice guides, standard operating procedure for DCP for member states, standard operating procedure for MRP for member states, etc. The most relevant to the issues in this case are (i) the guidance document that the CMDh committee has produced in relation to the best practice to follow for Decentralised and Mutual Recognition Procedures[19] and (ii) the CMDh guidance document that relates specifically to the DCP[20].

51 As noted above, Article 28 describes briefly the timetable for the DCP and the Notice for Applicants and the guidance documents produced by the CMDh which provide greater detail and insight into how the procedure is carried out. The CMDh has produced a flowchart explaining the DCP which shows how the time period of 210 days allowed for in Article 28 of the Directive is allocated and used. The CMDh best

[16] For full text of chapter see http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap2_2007-02_en.pdf.
[17] See http://www.hma.eu/
[18] See http://www.hma.eu/cmdh.html (there is also a corresponding group for veterinary products)
[19] See Best Practice Guide for the Decentralised and Mutual Recognition Procedures (April 2013)
[20] See Decentralised Procedure Members States' Standard Operating Procedure (January 2014).

practice guide[18] and standard operating procedure[19] describe what events need to occur, by when, what are the options available at each stage, depending on how the RMS, applicant and CMS interact. This flowchart is also included in Chapter 2 of Volume 2A - Procedures for marketing authorisation - of Volume 2: *the Notice to Applicants* (see Annex II, page 38) of "*The Rules governing Medicinal Products in the European Union*"[15].

52 I consider that it is necessary to be aware of the CMDh best practice guide[21] and standard operating procedure[22] as well as the explanation provided in Chapter 2 of Volume 2A of the Notice to Applicants[15] when considering the implications of this flowchart and its relevance to the case in hand.

Relevant Case Law

UK Courts – DuPont

53 In *EI du Pont de Nemours & Co v UK Intellectual Property Office* [2009] EWCA Civ 966, hereafter *DuPont,*[21] the court considered what is required in an application for a six-month extension to the duration of an SPC under EC Regulation 1901/2006, hereafter the Paediatric Regulation[22]. The relevant requirements are listed in Article 8(1)(d)(i) and 8(1)(d)(ii) of the SPC regulation. The court also considered the circumstances under which rectification under Article 10(3) could be used to address the deficiencies identified in such an application. The court concluded that where an irregularity with an application for an extension to an SPC under the Paediatric Regulation is identified by the Office, the applicant should be given an opportunity to rectify this irregularity after the date that the original application was made. In this case the date of application was 6 months before expiry of the original granted SPC to which a 6-month extension was sought, which under Article 7(5) of the SPC regulation was the latest deadline for making such an application[23].

54 The applicant had completed all the steps necessary in the UK to gain the 6 month extension to the SPC under the Paediatric Regulation – but was not able to provide confirmation that the MA had been updated in all the EU-MS to show the results of the tests carried out in the paediatric population. This is one of the key requirements

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[21] This was an appeal from the Patents Court (see *EI du Pont de Nemours & Co v UK Intellectual Property Office* [2009] EWHC 1112 (Ch)) which in turn was an appeal from the decision of the hearing Officer at the IPO (BL O/096/09, DuPont). (a) For full text of IPO decision *see IPO website at https://www.ipo.gov.uk/p-challenge-decision-results/p-challenge-decision-results-bl?BL_Number=O/096/09 or http://www.bailii.org/uk/cases/UKIntelP/2009/o09609.pdf);* (b) For full text of the Court of Appeal decision see http://www.bailii.org/cgi-bin/markup.cgi?doc=/ew/cases/EWCA/Civ/2009/966.html&query=title+(+du+)+and+title+(+pont+)&method=boolean.

[22] Regulation (EC) 1901/2006 of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for Paediatric Use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

[23] This 6 month deadline was the transitional arrangement when the Paediatric regulation first came into force and lasted for first five years this regulation was in force. This period is now over, and all such applications now have to be made 2 years before expiry of the SPC – see Article 7(4) of the SPC Regulation.

of the Paediatric Regulation[24]. This was based on the fact that not all the NCAs in each MS had completed the updating of the MAs for their territory. The Court of Appeal concluded that this evidence to show updated MAs in all MS could be provided after the date of the application and should not prevent the applicant from being able to obtain the 6 month paediatric extension to the SPC in the UK. I note in this regard that there was a fixed deadline for making the application for the extension i.e. 6 months before the expiry of the SPC (see Article 7(5) of the SPC Regulation). I note also that the court was concerned to make sure that the decision was delivered before expiry of the SPC because it was concerned that once an SPC has expired it cannot be extended. Finally, I also note that the applicant was able to provide all the necessary documents to show that all MAs had been updated in all MS before the expiry date of the SPC.

55 The *DuPont* case concerns whether or not it is possible for an applicant for an extension to an SPC to provide outstanding documents, in this case copies of national MAs from EU-MS outside the UK. These were not available when the deadline for the application for the extension passed but subsequently became available before the expiry date of the SPC. Under the Mutual Recognition Procedure (MRP) for updating the MA, once the competent authority from the RMS confirms that all the steps have been completed and that the MA has been updated with the results of studies in children and a statement of compliance, then the relevant competent body in each member state in the EU is responsible for issuing the updated national MA incorporating the results of the paediatric studies and including a statement of compliance with the agreed PIP for their territory[25]. A requirement for the reward under Art 36(1) of the Paediatric Regulation is that the applicant provides proof that the MAs in all EU-MS have been updated with the results of the paediatric studies and include a compliance statement to confirm this – see Articles 8(1)(d)(i) and 8(1)(d)(ii) of the SPC regulation. If a national competent authority in one MS was slow to carry out its task, i.e. if they took longer than the 30 day period provided for, this could have a significant effect on the ability of the applicant to show that they have met this requirement and so gain their reward, especially in those MS who had delivered the relevant updated MAs within this period. The court found that it was appropriate for the applicant to be able to provide various documents to supplement his application, i.e. to confirm that the medicinal product was the subject of an updated MA in all the EU member states, after the deadline had passed for the application for the extension.

56 The *DuPont* case has been referred to by both the examiner and the applicant in support of their respective arguments.

View of Applicant

57 As the applicant has completed all the practical work required – clinical tests etc. – and these have already been evaluated by the RMS and agreed with the CMS, then it is not appropriate for the applicant to be denied an SPC because the national

[24] See Articles 28 and 36 of the Paediatric Regulation and Article 8(d) of the SPC Regulation

[25] For an explanation of the authorisation procedures for medicinal products in the UK market via the national route under Directive 2001/83/EC or centralised route under EC regulation 726/2004, see the explanation and discussion in the original IPO decision concerning *DuPont* and the subsequent appeal hearings on this case – see footnote 24 above.

competent authority in the UK can take up to 30 days to issue the granted marketing authorisation.

58 The applicant has done all that he needs to and can do to meet the requirements of Article 3(b) of the SPC regulation. He can do no more! Thus, it is not right that he should be refused an SPC because the competent authority in the UK has not had time to issue the decision. It is inevitable that this decision will be issued and the text of the SmPC, the product information leaflet (PIL) and the package label (PL) are already known because they have been agreed by the RMS. This is why the RMS was able to issue the '*End of Procedure Communication of Approval'*, dated 10 September 2014.

59 The applicant provided the '*End of Procedure Communication of Approval'*, dated 10 September 2014, from the RMS within the deadline set for applying for an SPC, i.e. under Article 7(1) and before expiry of the SPC. The end of procedure letter indicates that a Marketing authorisation will be issued in each MS and the applicant should be allowed to provide a copy of this MA when it is available. The lack of a marketing authorisation was identified in the first examination report and the procedure under Article 10(3) is available to allow this lack to be rectified within the time period set.

View of Examiner

60 The examiners view is that Article 3(b) is not complied with insofar as, on the date this application was submitted, 12 September 2014, no MA had been granted for the medicinal product comprising the active ingredients for which an SPC is sought. Article 10(2) dictates that in such circumstances the application shall be rejected. The MA in the UK was granted on 10 October 2014.

61 Whereas the facts of this case share some similarities with *DuPont*, the examiner considered that, whereas *DuPont* provides that irregularities as regards Article 8 may be rectified having regard to Article 10(3), there is no such course of action provided with respect to Article 10(2), which refers to the substantive requirements for obtaining a certificate. Thus, *DuPont* is not on point. It is not that a granted MA existed at the date of application but was not correctly identified, it was rather than the MA did not exist at all. In this situation, this is a substantive failure under Article 10(2) and rectification under Article 10(3) in relation to such substantive requirements is not envisaged by the SPC regulation.

Analysis

62 Article 2 of the SPC regulation makes clear that a product that is protected by a patent in the territory of a MS and is subject, prior to being placed on the market as a medicinal product, to an administrative authorisation procedure as laid down in Directive 2001/83/EC can qualify for an SPC, if it meets the conditions laid down in this Regulation. The DCP is an authorisation procedure laid down under Directive 2001/83/EC – see above and Article 28 of the Directive.

63 The timings of various events that took place in relation to this SPC application are listed in Table 2 below. The events relating to the SPC, MA and basic patent are all

***Table 2*: Chronology of events in relation to the basic patent, marketing authorisations (MAs) and supplementary protection certificates (SPCs) which relate to Ezetimibe**

Date	Day #	Pat	MA	SPC	Event
14 Sep 1994		✓			Filing Date for Patent EP0720599
19 May 1999					Grant date for Patent
4 Apr 2003			✓		Grant date of MA for ezetimibe in UK, first MA in community granted in DE (17 Oct 2010)
18 Nov 2004			✓		Grant date of MA for ezetimibe and simvastatin in UK, first MA in community granted in DE (2 Apr 2004)
9 Jun 2003				✓	Filing date of SPC application SPC/GB/03/023 in UK (for ezetimibe)
23 Oct 2003				✓	Grant of UK SPC/GB/03/023 in UK
18 Feb 2005				✓	Filing date of the SPC application SPC/GB/05/010 in UK (for ezetimibe and simvastatin)
30 Jun 2006				✓	Grant of UK SPC SPC/GB/05/010 in UK
Sep 2006			✓		MSD begins experiments to develop a combination treatment of ezetimibe and atorvastatin
2006-2013					Development of a formulation of a fixed dose of ezetimibe and atorvastatin in tablet form. Various generations of formulations [Gen#1 (2006); Gen#2 (2009): Gen#3 (abandoned 2011); Gen#5 (Mar 2011) & Gen#6 (Jun 2011)] were developed and tested in animals and humans for bio-equivalence, clinical equivalence, stability and compatibility
Sep 2012			✓		Request to Germany to act as RMS for 2013 submission of application for MA for ATOZET under DCP
Sep 2013	0		✓		Submission of ATOZET marketing authorisation application under DCP to DE and other EU Countries
10 Sep 2014	209		✓		End of Procedure approval decision for ATOZET issued by BfArM in Germany (RMS)
12 Sep 2014			✓		Grant of the first EU marketing authorisation for ATOZET in France
12 Sep 2014				✓	Filing date of the SPC application SPC/GB/14/062 in UK
13 Sep 2014		✓			Patent expiry
14 Sep 2014					Entry into force of SPC/GB/03/023 in UK (for ezetimibe); Entry into force of SPC/GB/05/010 in UK (for ezetimibe and simvastatin)
17 Sep 2014				✓	Examination Report from the UK IPO
10 Oct 2014	239		✓		Grant of the UK marketing authorisation for ATOZET
17 Nov 2014					French and UK marketing authorisation filed at the UK IPO
18 Nov 2014					Deadline given by UK IPO in the examination report dated 17th September for correcting irregularities of the application

Included, as are the corresponding deadlines in relation to the Assessment Step II and National Step under the DCP for ATOZET

64 The question in this instance is has the medicinal product ATOZET, which is a combination of ezetimibe and atorvastatin, actually been subject to an authorisation procedure under the directive, because on the date that the SPC was applied for, the authorisation process was not complete. There still remained a final stage to be completed before a marketing authorisation was granted for ATOZET in the UK. In their skeleton argument and at the hearing, the applicant emphasised on a number of occasions that the applicant had completed everything that they were required to do under the DCP and that this has been examined and then approved by the RMS within the timetable set down in the Directive, i.e. completed on day 209 out of 210. The applicant provides evidence and confirmation of this by providing the '*End of Procedure Communication of Approval'*, dated 10 September 2014, issued by the BfArM, the German competent authority acting as RMS for this decentralised procedure.

65 The applicant made reference to the flowchart outlining the DCP (see above and Annex 1) in the material they provided with their skeleton argument in advance of the hearing. They provided a version of the flowchart adapted from that in Chapter 2 of Volume 2A of the Notice to Applicants[26] outlining how the DCP worked in relation to the authorisation for ATOZET. They also included a copy of Chapter 2 itself making specific reference to the sections dealing with Assessment Step II, Finalisation of the procedure and Granting of the national marketing authorisations (see Sections 4.3.3, 4.3.4 & 4.4). Based on this material, the applicant argues that the only remaining step to be completed before an MA can be issued in each MS is a purely administrative step; i.e., the competent body in each MS has to take the mutually agreed version of all the documents sent by the RMS and issue these as part of the granted MA for that member state. The applicant also asserted that as this procedure was conducted in English there is no need for translations of the approved documents – as identified and confirmed by the RMS. Thus, in UK, all that needs to happen before the issue of the granted MA is some form of administrative or bureaucratic step that does not involve any decision making. The applicant stated that the fact that the French NCA was able to issue the granted MA in France within 2 days of the '*End of Procedure Communication of Approval'*, dated 10 September 2014, issued by the RMS, merely confirms that this is the case. Thus, as the applicant has completed everything they need to do before the deadline for applying for an SPC – in this instance before the expiry of the SPC – they should be allowed to update their application with the relevant national authorisation for the UK as soon as it is produced within the 30 day period set down by the Directive.

66 On the face of it this seems a compelling argument. In order to obtain a benefit or reward, the applicant has to complete a whole series of steps – in this case – gather evidence, carry out tests and provide analysis to show that the product for which they are seeking a MA does, in fact, have a beneficial therapeutic effect and a positive risk-to-benefit profile. The applicant cannot obtain the reward until these steps are complete but once they are completed and once they are verified or confirmed by an appropriate NCA as being of value and meeting the requirements set down, they should be entitled to the reward. If the only outstanding step is the

[26] See footnote 16 above

need for the results of this approval process to be published and made available in each MS and involves nothing more than making approved texts and information available in a form that people in that territory can read, then it would not be right to refuse the benefit to the applicant because one member state has been slower than another to make this information available.

67 However, in order for this argument to be acceptable it is necessary for me to consider if the situation is as straightforward as the applicant describes it. It appears to me that I have to give some consideration to what is the effect of accepting the '*End of Procedure Communication of Approval'*, dated 10 September 2014, as confirmation that the issue of an MA is inevitable. Does this raise any questions regarding what will be the date that the granted MA takes effect in the UK? Will it have any impact on when the applicant will be able to put the product on the market if I accept, as I am being asked to do, that the MA is, for all practical reasons, complete and can be granted once the RMS issues an '*End of Procedure Communication of Approval'*, to the applicant?

Status of the 'End of Procedure Communication of Approval' from RMS

68 As the applicant has made clear in their skeleton argument there is an agreed timetable and procedure for dealing with applications in the DCP. This procedure can take a total of 210 days (see Article 17 and Article 28 of the Directive). From the copy of the email entitled "*FW: DE/H/3895-3898/01-04/DC Atozet et al - D209 End of Procedure documents*", which is the the applicant points out that on day 209, the RMS issued this email to indicate that the decentralised procedure – identified by this reference number – had been completed on day 209, i.e., 1 day early.

69 The applicant characterised this document as an instruction to the competent authorities of all CMS to issue a national MA valid in their territory for the medicinal product ATOZET. Although the applicant did not provide copies of the attachments to this email as well as the email itself, they did state that these attachments were the final agreed forms of the documents necessary for each competent authority to be able to issue an MA, i.e. SmPC, PIL and package label. The applicant has to provide translations of these documents into the relevant languages of all the CMS that are involved in this decentralised procedure. The explanation of the DCP indicates that any such translations should be provided within 5 days of the notification of the end of procedure communication. The competent authorities in each MS have to issue the MA using the agreed documentation within 30 days of the end of procedure i.e. between Day 211 and Day 240. This latter timing is clear from Article 28(5) of Directive 2001/83/EC.

70 The flow chart for the DCP and the associated guidance in the Notice of Applicants and the CMDh Standard Operating Procedure – see Flowchart in Annex 1 to this decision - is the version from which the condensed version of the flowchart cited by the applicant in their skeleton argument is derived. The version provided by the applicant in their skeleton focuses specifically on the procedure that takes 210 days for the RMS to complete its work and an additional 30 days for all the MS (CMS and RMS) to issue granted MAs. The original version also includes some additional variations that will impact on the final timing when the MA will be granted, i.e. when the 30 day period for issue of the granted MAs will occur. These variations occur in the second assessment step (Assessment Step II) and can impact on when the final

national step will start. In all instances the national step is the final step of the DCP and provides for 30 days for the RMS and CMS to grant the MAs based on the documents agreed and approved by the RMS at the end of the Assessment Step II phase. I note that in all cases, the final step involving issue of the granted MA is set for a 30 day period – as laid down in Article 28(5) of the Directive.

71 I have considered this material carefully and the arguments made by the applicant in this regard and consider that I am being asked to make a distinction between two parts of the DCP – Assessment Step II and the National Step. The applicant is asking me to place a greater emphasis on one part of this process – the Assessment Step II phase where the role of the RMS in securing agreement to the final form of the SmPC, PIL and package label is essential and its conclusion is marked by the RMS issuing the '*End of Procedure Communication of Approval'*, such as that dated 10 September 2014 in this case. I consider that although this RMS-led phase is clearly an important and essential part of the process and may well involve the RMS having to interact a lot with the applicant and CMS to get the final form of the documents necessary for granting an MA agreed (i.e. SmPC, PIL and package label) it is not the final part of the DCP in my view. The closure or conclusion of this Assessment Step II is not a decision, in my view, it is a confirmation of what has been agreed in that step and indicates to all those involved in the DCP that they can issue a decision to grant an MA based on the mutually recognised and approved documents. The actual issuance of a granted MA in each MS is the final part and the directive specially provides for this final step requiring that "*each Member State ..... shall adopt a decision in conformity with the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved, within 30 days after acknowledgement of the agreement*."

72 Mutual recognition procedures are based on national systems for authorisation of medicines for human use, i.e., the national legalisation in each MS that gives effect to Directive 2001/83/EC. Directives do not have direct effect; they have to be implemented into national legislation. Thus approval under the Directive in the UK is made via the Medicines for Human Use (Marketing Authorisation etc.) Regulations, SI 1994/3144, as amended. This is the basis on which the MHRA is able to give effect to the *End of Procedure Communication of Approval* provided by the RMS within the 30-day national phase.

73 An MA holder in the UK cannot put a medicinal product on the market in the UK until the MA has been granted in the UK. This grant takes the form of a letter from the MHRA and the date of this letter is the date from which the product can be put on the market in the UK. The SmPC – approved in the DCP – accompanies this decision but is not the decision in its own right. I have considered the documents from the MHRA provided by the applicant which show that the MA was granted in the UK on 10 October 2015. This MA was granted within the 30 day period set down in the Directive using the documents provided by the RMS in its '*End of Procedure Communication of Approval'*, dated 10 September 2014.

74 The MA grant documents for the UK provided by the applicant comprises a set of three documents – two cover letters and the certificate of grant. The two cover letters are addressed to a named individual at MSD with an Address in Belgium who submitted the MA application. Each of these letters is entitled "GRANT / RENEWAL OF MARKETING AUTHORISATION" and identifies the exact form of the product that they

apply to e.g. ATOZET 10mg/10mg, film coated tablets as well as the type of procedure used (in this case, decentralised) and the EU procedure number (in this case, it is the same procedure number as the RMS refers to in the End of Procedure Approval email – DE/H/3895/001/DC). They also give the MHRA reference for the granted marketing authorisation for this specific product – in this case PL00025/0618-0001. The first letter includes the following two statements:

> "The Licensing Authority agrees to the grant or renewal of the marketing authorisation for the above submission on the basis of the data provided. This includes any replacement and amendment of the original dossier."

and

> "The formal documents are enclosed. These constitute evidence of authorisation. If you consider them to contain information that is incorrect or not in accordance with the dossier, please return immediately indicating any errors."

The second cover letter, while containing the same information in relation to the exact form of the product, the type of procedure used, the EU procedure number and the MHRA reference for the granted marketing authorisation for this specific product, also makes reference to the fact that the application has been granted on the basis of the harmonised test agreed during the procedure for approving the package label and product information leaflet (PIL). However, it also indicates that "*In accordance with the medicines legislation, the product shall not be marketed in the UK until prior approval of the product labelling and leaflet mock-ups has been obtained.*" It provides some additional information to the addressee on how to meet the requirement for product information according to UK procedures under Article 61(3) of the Directive

75 The third document in this set is the certificate of grant of the marketing authorisation. It is headed "*The Medicines for Human Use (Marketing Authorisations etc.) Regulations, SI 1994/3144, as amended*" and *GRANT / RENEWAL OF MARKETING AUTHORISATION*. It does not refer to the type of procedure used, the EU procedure number and the MHRA reference for the granted marketing authorisation for this specific product. It does refer specifically to both the exact product covered (in this case ATOZET, 10mg/10mg, film coated tablets) and names the party to whom the authorisation is granted, in this case, MSD Ltd with a UK address. It then goes on to state the following:

> "This Marketing Authorisation, under the above reference number is hereby granted I renewed in respect of the product named above. The Summary of Product Characteristics of the product is set out in the attached document.
>
> The application is subject to the further provisions set out or referred to in the above Regulations.
>
> This Marketing Authorisation, as now granted / renewed, unless previously revoked, will continue in force until the expiry date (if applicable) given below.
>
> Grant Date: 10/10/2014
>
> Date of Expiry: 10/09/2019"

76 Thus, I am not satisfied that the final step of the decentralised procedure, the national step, can be separated out in the manner proposed by the applicant as being purely administrative and inevitable.

77 The applicant argued that the DCP concludes with the end of Assessment Step **II** and the agreement recorded by RMS – see Article 28(4) of the Directive and the flowchart in Annex 1, in effect, stating that the National Step is separate because it does not involve any of the interaction between the CMS and RMS and the applicant – that is all over and complete when the RMS issues the *End of Procedure Communication of Approval*. However, I am not persuaded by this because, although the *End of Procedure Communication of Approval* issued by the RMS signals the end of interactions between CMS and RMS using the mutual recognition approach, until the NCA in each MS actually issues a granted MA – see Article 28(5) – which includes the mutually agreed SmPC, PIL, and the mutual agreed package label, there is not a valid authorisation according to the Directive in force in each MS. As recitals 12 and 13 and Article 28 of the directive, in particular, refer, the overall objective of the DCP is to provide granted marketing authorisations for medicinal products in each MS based on the principle of mutual recognition. The stage of the MA granting process reached at the end of Assessment Sept **II** does not deliver this. In my view, delivery of the granted MAs by the appropriate NCAs in each member state is an important part of the overall process and indicates its completion. This is clear from its inclusion in Article 28 of the Directive – see Article 28(5).

78 The witness statement of David DeTora gave a detailed explanation of the steps taken by MSD in the development of ATOZET. Research to develop a combination treatment of ezetimibe and atorvastatin began in 2006 when there was a period of 8 years protection remaining in the life of the granted patent. At that time, two SPCs had already been granted for products based on this basic patent (see Table 2 and below). Work on ATOZET did not begin early in the life of the patent, it began only after the work on a monotherapy and a combination of ezetimibe with a different statin had been completed. Thus, it is clear that the applicant already had a wealth of experience and knowledge in relation to ezetimibe and how a combination of ezetimibe with a statin – in this case, simvastatin – worked. In his witness statement, Mr DeTora indicated that the work on ezetimibe and atorvastatin had to take account of the compatibility and interactions of the two different drugs in this combination, and that this was sufficiently different that the tablet had to be developed as a bi-layer with each drug in a separate layer of the tablet. The stability and pharmaco-kinetic behaviour of atorvastatin when in combination with ezetimibe proved complicated and needed significant investigation. This led to the creation of 6 different generations of fixed dose combination formulations of ezetimibe and atorvastatin which were all subject to a greater or lesser degree to studies on bio-equivalence, clinical equivalence, stability and compatibility. As was stated in the witness statement, the stability of each formulation took some time to investigate. Mr DeTora indicated that each such stability study on a formulation will require at least one year per study.

79 In this case, the steps taken by the applicant to gain approval for the combination of ezetimibe and atorvastatin began with only eight years left on the life of the patent and it appears that obtaining a suitable combination of both active ingredients was not that straightforward given the need to develop a bi-layer tablet. Thus the

applicant has taken more time than maybe they expected would be necessary to obtain a suitable form of the combination and gain approval for it. This meant they were ultimately left with a situation, unlike that they experienced with the two earlier medicinal products based on this patent, where the usual 30 day period allowed for issuing a granted MA under the DCP did not all fall with the period of protection covered by the basic patent. The patent expired three days after the issue of the *End of Procedure Communication of Approval'*, dated 10 September 2014. The MHRA still had 27 days of the 30 day period within which to issue the MA.

80 The applicant considers that although the granted MA was issued after expiry of the patent, the fact that the application for the MA in the UK was made before this expiry date and the fact that the directive and associated guidance indicates that an MA will be issued by the CMS, providing the actual details of the granted MA after the date of application is allowed on the basis of *DuPont*. They consider that it does not meet the objective of the SPC regulation, as indicated by recitals 2-7, if the applicant is not able to obtain an SPC in recognition of the delay it has experienced in gaining the regulatory approval for ATOZET. The applicant has to carry out all the regulatory work in advance, which it has done and has completed all this work and secured the agreement and approval of the RMS to the SmPC, PIL and the package label before the patent expires. It is clear to all third parties that the substantive work is now complete and only the formal granting of the MA is required by the RMS and CMS. Updating the application with the necessary details about the granted MA in the UK after the date of application for the SPC rectifies the deficiency identified by the examiner with this application. At the time of application, it is clear that an MA in the UK would be granted, it is just that the formal details, e.g. identifying a product licence number, issuing a certificate of grant etc, had not been completed to go along with the mutually agreed version of the SmPC, PIL and the package label.

81 At the hearing the applicant advanced a number of additional points to support their argument that they should be allowed to supplement i.e. rectify their application for an SPC in the UK after the expiry date of the patent with the details of the granted MA in UK:

(i) Third parties will not be disadvantaged because this patent is already the subject of two other SPCs which will come into force when the patent expires, thus no third party will be prevented from doing anything or placed at any further disadvantage than they are already if this SPC is granted. For example, the SPC for the monotherapy would prevent any third party for bringing a combination of ezetimibe with any other active ingredient to market.

(ii) In his first official exam report, dated 17 September 2014, the examiner set a date of 18 November 2014 by which time any irregularities identified in the application should be addressed. The applicant provided a copy of the granted UK Marketing Authorisation, issued on 10 October 2015, within the 30 day national phase period for DCP, before this deadline expired. By analogy with *DuPont*, why identify a deficiency and set a deadline for response if it is not accepted that the deficiency can be dealt with?

(iii) The first MA for the ATOZET, the combination of ezetimibe and atorvastatin, in the Community was that issued by France on 12 September 2015, two days after the end of procedure communication had been issued by the RMS, and one day before the patent expired in the UK. Thus the duration of any SPC in the UK (which is calculated using Article 13 of the SPC Regulation) will be calculated using this MA which was granted before expiry of the SPC. It is sufficient to know that an MA will be granted in the UK, it is not so important to know when it will be granted in the UK because it is not relevant for the purpose of working out the duration of the SPC.

(iv) The procedure for approval of this application was conducted in English and thus all the documents which the RMS approved and recommended to the CMS in the *End of Procedure Communication of Approval* were all in English. Thus there is no need for a translation of documents to be submitted in the national step, as recommended by the flowchart and related guidance, thus there is noting that can happen, in UK (at least), to prevent the mutually agreed SmPC, PIL and package label sent by the RMS with the '*End of Procedure Communication of Approval'*, dated 10 September 2014, from being used directly in the granted UK MA. These mutually agreed documents were sent to MHRA (the NCA representing UK as CMS) before expiry of the patent and before the application for the SPC was made. The applicant suggested that all the MHRA had to do was basically make a copy of these documents and include them with the UK grant certificate.

82 It is the case that there will always be differences between when MAs are granted in each MS which reflects the different ways that the government of each MS chooses to deliver this function in their national administration. The SPC regulation recognises this and provides, for example, under Article 13 that account is taken of when the first MA in the European community was granted to work out the duration of the SPC. The SPC regulation also recognises that MS may chose to implement it only in relation to Article 3(a) and 3(b) – see Article 10(5) of the SPC Regulation. However, it appears to me the impact of the approach being proposed by the applicant is that all the MAs would be deemed to take effect from the end of procedure approval step – this would be the same date in all MS. However, this fails to take account of the fact that each country has to grant the MA in a manner that takes legal effect in their country and has a date of legal effect that can be determined.

83 If the applicant can supplement the application in the way they propose what they are saying is that *de facto* the MA application is effective from the date of the end of procedure approval email from the RMS but that until the MA is actually granted in the Member State concerned by its NCA then it does not actually have legal effect. I find this comparison between when something is approved and when something can have legal effect to be an interesting one. The CJEU has recently ruled in *Seattle Genetics, C-471/14,* that the date when a Marketing Authorisation issued by the EMA takes effect is not when the decision is approved but rather when the holder of the marketing authorisation can actually put the product on the market based on the centralised MA issued by the European Commission, i.e. the date the holder

receives notification that the MA has been granted[27]. This judgment confirms the view of this Hearing Officer in IPO decision BL O/418/13, *Genzyme*,[28] that the key to determining the duration of an SPC is the date upon which the holder of the marketing authorisation could actually sell the product for human use. This date is that when the holder of the MA receives notification of the decision by the European Commission to grant the MA and not the date that the decision is approved or granted by the Commission.

84 Reflecting further on the implications of either: (a) accepting the *End of Procedure Communication of Approval* from the RMS as evidence that a MA has been granted; or (b) accepting the *End of Procedure Communication of Approval* from the RMS as a marker that an MA will be granted in the UK within the next 30 days and the application will need to be supplemented with these details, causes a problem in terms of the overall duration of the SPC, in my view. If the *End of Procedure Communication of Approval* is considered as evidence that a MA has been granted then it is hard to avoid a conclusion that this is the effective date for the MA, and the holder will benefit by an additional period of protection, up to 30 days additional term of protection than they are entitled to under the SPC regulation as it is not very likely that a NCA will be able to issue a granted MA on the date that the *End of Procedure Communication of Approval* is issued. There will always be some delay between (i) notification by the RMS to the CMS that the SmPC, PIL and package label have all been agreed and (ii) the actual issue of the granted MA in each CMS and the RMS by the relevant NCA. In this case, the NCA in France was the first to issue a granted MA in the community, so this delay is relatively speaking short, a time difference of 2 days.

85 If the *End of Procedure Communication of Approval* from the RMS is considered as a marker that an MA will be granted in the UK within the next 30 days so that the applicant can submit an application for an SPC before expiry of the patent and that this application will need to be supplemented with these details, you still have a similar problem, in my view. When the MA is issued in the UK within this 30 day period, the effective date of the MA although it still falls within the 30 day period set by the directive, it falls outside the expiry date of the patent. In this instance, the MA effective date falls on a date after the expiry of the patent. If I was to accept the proposal that the applicant can supplement the application they made before the expiry of the patent with the MA that is granted after the expiry date of the patent, then I am Ieft with the problem of deciding if an SPC can be granted and, if so, what is the duration of the SPC and what is the effect of this gap between the expiry date of the patent and the effective date of the MA. If I accept the *End of Procedure Communication of Approval* as notification of grant or as a marker that grant will be forthcoming, how can I avoid also accepting it as evidence of the earliest date that the MA has been granted in the Community and hence it's use to calculate the duration of the SPC. As I have noted above, this leads to the applicant gaining up to as many as 30 extra day's protection.

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[27] Seattle Genetics Inc. v Österreichisches Patentamt., Judgment of the CJEU (Eighth Chamber) of 6 October 2015. See full-text of decision at http://curia.europa.eu/juris/document/document.jsf?text=&docid=169197&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=991355

[28] See text of decision at https://www.ipo.gov.uk/p-challenge-decision-results/p-challenge-decision-results-bl?BL_Number=O/418/13 or http://www.bailii.org/uk/cases/UKIntelP/2013/o41813.pdf

86 Thus, I consider that in order to have the basis for a valid SPC application in the UK under Article 3(b) of the SPC Regulation, the applicant needs to have a granted marketing authorisation in the UK at the date of the application for the SPC.

The relevance of the DuPont Decision and Article 7 of the SPC Regulation

87 The agent considered that the *DuPont* case provides a strong basis for the applicant being able to rectify their application after the date of application and within the period set by the examiner. Mr Horgan dealt with this at length in his skeleton argument and again at the hearing. He considers that this decision provides that any irregularity identified with an application can be rectified after the date of application.

88 The applicant refers to the fact that the irregularity that has been identified is that the details of the valid MA in the UK have not been provided with the application on the date that the application was made. However, the end of procedure approval email was provided on this date and this serves to make clear that an MA in the UK will be granted within the next 30 days. Thus there is a valid MA for the UK it is just that they do not have the detail yet but will be able to provide them within 30 days at most. This 30 day period falls within the time period set by the examiner to respond to the examination report and correct any irregularities, so the applicant is satisfied that they can provide this information within this time period. This they consider is entirely consistent with the situation envisaged by the Court of Appeal in the *DuPont* case. The irregularity in this case is one that is administrative and not substantive – the proper identification of the MA in the UK – as distinct from the contention of the examiner which is that there is not a valid MA in the UK on the date that the SPC application was made. This I consider is the difference in interpretation between the examiner and applicant on which this question turns. If as is argued by the applicant, the end of approval notification from the RMS is sufficient to show that there will be an MA in the UK, in my view, this leaves the question of when the MA takes effect in the UK unanswered. If the competent authority in any CMS issues a granted MA before the expiry date of the patent in the UK, then it is clear that the duration of the SPC will be calculated based on this date, because this is the date of the first approval to place the product on the market in the Community (see Article 13). However, although that is correct as far as it goes, it is ignoring or skipping or glossing-over the requirement that in order to have an SPC in the first place in the UK, you must have a granted MA that is valid in the UK on the date that the application is made. Determining the duration of an SPC in the UK is only worked out once it has been established that there is the basis for granting an SPC in the UK in the first place!

89 The examiner makes a distinction between an irregularity identified under Article 10(3) which refers specifically to such an irregularity being the failure to meet the requirements of Article 8. This article, entitled 'content of the application for a certificate', lists what an application for an SPC should contain – see Article 8(1)(a)-(c) – and what an application for an extension to a certificate should contain (whether filled at the same time or at a different time) – see Article 8(1)(d), 8(2) and 8(3). The final part, Article 8(4), provides that a fee may be payable for a certificate and an extension to a certificate. The irregularities that arise in this situation are ones such as failure to provide a name and address, failure to provide the number of the basic patent, number and date of the authorisation granted in that member state and/or the number and date of the first marketing authorisation granted in the community. Of

particular interest is Article 8(1)(b) which requires that the applicant include a copy of the authorisation to place the product on the market, as referred to in Article 3(b), which identifies the product, and the number and date of the MA but also includes the summary of product characteristics (SmPC).

90 The applicant considers that the above irregularities are more administrative in nature and not substantive. Article 3 lays down the substantive requirements for the grant of an SPC and Article 10(2) indicates that if these are not met then the application for a certificate should be rejected. The reference to paragraph (3) in Article 10(2) indicates that the applications should not be rejected for failure to meet the requirements of Article 8 without having an opportunity to rectify this failure.

91 Not having a valid marketing authorisation at the date of application under Article 3(b) is different to making a mistake in providing the details of a valid authorisation as part of the application. The examiner considers that Article 10(3) allows the latter to be rectified after the date of application but not the former.

92 In reflecting on these different points of view and the *DuPont* decision, I consider that there is a difference between an application for a certificate and an application for an extension for a certificate. An application for a certificate is governed by Article 7(1), and 7(2) whereas the application for a paediatric extension is governed by Articles 7(3), 7(4) and 7(5). Consideration of these provisions indicates that there is a clear difference between when an application for a certificate is made and when an application for an extension is made. An application for a certificate can only be made after two events have already occurred – the grant of the patent and the grant of a marketing authorisation. Both of these essential elements must be available. The applicant has to wait until both events have occurred and then they have a period of six months to apply for the certificate. In contrast, an application for an extension to a certificate has to be made or submitted before an event occurs. It must be made two years before the expiry date of the certificate (or in the earlier transition period which has now passed - but was the situation in the *DuPont* case – six months before expiry of the certificate). Thus an applicant for a certificate and an applicant for an extension are in two different situations.

93 The *DuPont* case concerned an application for an extension to an SPC and not an application for an SPC. The court considered that the applicant had to make an application by a specific date whether it had all the relevant materials or not in order to obtain an extension to the SPC. If no application was made by this date, no extension could be obtained. At the deadline date, i.e. six months before the expiry of the certificate for Losartan, *DuPont* did not have a copy of all the updated marketing authorisations in all member states showing the compliance statement confirming that the results of all the paediatric tests had been included in the (updated) SmPC that was part of the updated MA. They did however have all the relevant materials for the UK, i.e. a copy of the marketing authorisation for the UK with the updated results from paediatric testing and the inclusion of the relevant compliance statement. However, as noted above, to gain the reward of a six month extension to the SPC an updated MA in UK is not only required, but one also has to provide evidence that the MAs in <u>all</u> EU-MS have been updated. It was this latter requirement that had not been completed before the applicant had to apply for the extension. The court considered that as some NCAs in some MS were taking longer than the 30 day period provided for in the Paediatric Regulation and the Directive for

issuing the updated MAs with the compliance statements, then the applicant should not be denied the reward in the UK and that he should be able to provide copies of these updated MAs after the deadline for making the application for an extension to a certificate.

94 In *DuPont*, the court was clear that the applicant for an extension should not be prevented from having the reward they were entitled to because of the failure of the relevant NCAs to complete, within the time period set down in the legislation, the step to issue an updated MA with the relevant compliance statement and an attached SmPC with details of the outcomes from the paediatric testing carried out included therein. This is not the situation in the present case; under the DCP, each NCA has 30 days to issue a granted MA for their territory and so complete this final step. The NCA in the UK, the MHRA, did complete this step within the time period set down in the Directive, i.e. 30 days. As a result, I do not consider that the applicant is being put in an adverse situation. The time table for the DCP was followed and delivered a valid authorisation under the Directive, as implemented in UK law. In the present case, in contrast to the situation in *DuPont*, the procedure to deliver the granted MA in the UK does not appear to have fallen outside the timetable laid down under the Directive, and the related guidance, of which everyone is aware and can plan for accordingly.

95 The point made by the applicant in relation to the fact that the DCP was conducted in English and so there is no concern about translations as any third party in the UK will know what the MA and its associated SmPC will cover is not relevant in my view. The procedure recognises that there is a need for translations to be provided to NCAs by the applicant in order to for them to obtain granted MAs in all member states. The DCP recommends that the applicant send any such translations within 5 days of the end of procedure approval notice to those MS where a translation into the official language of that state is required. Meeting this 5 day deadline, means that the NCAs will in turn be able to meet the 30 day deadline to issue the granted MAs for these member states. While it seems rare that a problem will arise at this stage, it can do so and the procedure does allow for translation issues to be dealt with within this period. Thus there may be some additional work between applicant and NCA at this stage to ensure that an MA is granted. This is one reason why the granted MA may be issued at different dates within the 30 day National Step period. However, the work necessary to grant the MAs, whether translations are required or not, has to be completed within this 30 day period.

96 I do not know if the applicant had the option to ask the MHRA to produce the granted MA more quickly than it did because no translations were necessary in UK and because of the proximity of the patent expiry date and deadline for application for an SPC? Nothing in the materials provided to me at the hearing or in the correspondence with the examiner suggests that the applicant considered or enquired if it was possible for the MHRA, or other NCAs, to issue granted MAs for their territory before the expiry date of the patent which corresponded to the 3rd day of the 30 day period within which NCAs have to issue the granted MAs. While, it is the case that the French NCA did issue the granted MA in France very early in the 30 day National Step period and the NCA in the UK did so later in this period, both bodies did so within the period laid down in the directive.

Conclusion

97 I consider that at the date that the application for an SPC was made, the applicant did not have a valid authorisation granted in accordance with Directive 2001/83/EC, to the place on the market in the UK, the medicinal product ATOZET, comprising the combination of active ingredients for which the SPC has been applied for (ezetimibe and atorvastatin). The information provided by the applicant i.e. the *End of Procedure Communication of Approval'*, dated 10 September 2014, provided by the RMS, does indicate that the Summary of Product Characteristics (SmPC), the product information leaflet (PIL) and the package label (PL) have been agreed. However, it still remains for the MA to be granted and for the date to be confirmed, by the appropriate authority (the MHRA), on which the medicinal product (comprising the combination of active ingredients for which the SPC has been applied for) can be placed on the market in the UK. The latter is the primary purpose of the MA and everything else – grant of SPC, duration of SPC etc – can only occur or be worked out once the MA has actually been granted.

Does the application comply with Article 3(c)?

98 In case I am in error in my conclusion above in relation to Article 3(b), that there is not a valid MA for the combination of ezetimibe and atorvastatin, I will consider whether or not the present SPC application meets the requirement of Article 3(c) of the SPC Regulation.

99 The issue under consideration is whether the SPC application for ezetimibe and atorvastatin can be granted using the same basic patent as the earlier (granted) SPCs for (i) ezetimibe or (ii) ezetimibe and simvastatin? Does the grant of these earlier SPCs mean that the product for which the SPC is currently being sought – ezetimibe and atorvastatin – is precluded because it has already been the subject of a granted SPC?

The Relevant Law

The SPC Regulation[7]

100 It is a well established principle of EU law, as noted above in relation to the discussion with regard to Article 3(b), that such law is defined having regard to both the purpose of the legislation - as set out in the recitals - and the articles which provide the substance of the law. I reproduce those sections of the regulation[29] – recitals and articles - that I consider relevant below (with my emphasis added in **bold**):

[29] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the Supplementary Protection Certificate for Medicinal Products, see OJ L 152, 16.6.2009, p 1. As explained in recital (1), this regulation codified and superseded Regulation (EEC) No. 1768/92 concerning the creation of a Supplementary Protection Certificate for Medicinal Products.

101 Recitals 2-5, 9 and 10 of the SPC Regulation state (emphasis added):

> *'(2) Pharmaceutical research plays a decisive role in the continuing improvement in public health.*
>
> *(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.*
>
> *…*
> *...*
>
> *(9) The duration of the protection granted by the certificate should be such as to provide adequate effective protection. For this purpose, the holder of both a patent and a certificate should be able to enjoy an overall maximum of 15 years of exclusivity* ***from the time the medicinal product in question first obtains authorisation to be placed on the market in the Community****.*
>
> *(10)* ***All the interests at stake, including those of public health, in a sector as complex and sensitive as the pharmaceutical sector should nevertheless be taken into account****. For this purpose, the certificate cannot be granted for a period exceeding five years.* ***The protection granted should furthermore be strictly confined to the product which obtained authorisation to be placed on the market as a medicinal product****.'*

102 Article 1 of the SPC Regulation provides the definition of 'product ' and 'medicinal product' as follows:

> *For the purposes of this Regulation, the following definitions shall apply:*
>
> *(a) 'medicinal product' means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;*
>
> *(b) 'product' means the active ingredient or combination of active ingredients of a medicinal product;*
>
> *.....*

103 Article 2 of the SPC Regulation defines the scope of the regulation (emphasis added) and reads:

> ***Any product protected by a patent in the territory of a Member State and subject, prior to being placed on the market as a medicinal product, to an administrative authorisation procedure as laid down in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use*** *or Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code*

relating to veterinary medicinal products ***may, under the terms and conditions provided for in this Regulation, be the subject of a certificate****.*

104 Article 3(c) of the Regulation defines the conditions for obtaining a certificate (emphasis added) reads as follows:

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;

(b) ...

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

(d) ...

The Relevant Case Law

Court of Justice of the European Union (CJEU)

Sanofi, C-443/12

105 In *Sanofi*, C-443/12*,* a preliminary reference to the CJEU from the UK court[30], the CJEU considered two questions. While the first question referred (in relation to Article 3(a)) is not relevant to the present case, the second question referred is:

"*In a situation in which multiple products are protected by a basic patent in force, does [the SPC] Regulation, and in particular Article 3(c), preclude the proprietor of the patent being issued a certificate for each of the products protected?*"

The court, based on its consideration of the overall purpose of the SPC regulation and a consideration of the relationship between the products in the combination and the innovation described and claimed in the patent; concluded:

"*the answer to the second question referred is that, in circumstances such as those in the main proceedings, where, 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 entitling him to oppose the use of that active ingredient, either alone or in combination with other active ingredients, Article 3(c) of Regulation No 469/2009 must be interpreted as* ***precluding that patent holder from obtaining – on the basis of that same patent but a subsequent MA for a different medicinal product containing that active ingredient in conjunction with another active ingredient which is not protected as such by the patent – a second SPC relating to that combination of active ingredients****.*"

[30] Reference for a preliminary ruling from United Kingdom, High Court of Justice (England & Wales), Chancery Division, made by decision of that court of 21 September 2012, received at the CJEU on 3 October 2012.

106 In reaching this conclusion the CJEU noted that the proceedings before the national court making the reference (the UK Courts) involved a situation not previously considered by the CJEU in that, on this occasion, they were dealing with a patent that protects a number of products within the meaning of Article 3(a) of the SPC regulation. This was in contrast to the situation previously considered in the *Biogen, C-181/95,* and *AHP, C-482/07,* judgments of the CJEU where the proceedings related to the situation where the same product is protected by a number of different patents and they concluded that only one of these patents can be used to obtain an SPC for this product.[31] In *Sanofi*, the first product already the subject of an SPC, was the monotherapy based on irbesartan, and the second product for which an SPC had been applied for was the combination therapy of irbesartan and hydrochlorothiazide (HCTZ). The court stated that, an SPC cannot be obtained for the second product as the earlier SPC granted for the first product provided the holder with the ability to oppose, on the basis of the basic patent, the use of this product (irbesartan) in the form of a medicinal product consisting of such a product or, (more importantly) containing it. In this new situation, where the same patent has the potential to serve as basic patent for two (or more) products, then it is not possible for the patent to be used as the basic patent for the second (or further) product, if the first or earlier SPC also provided the ability to protect this product. The court made clear at paras 39-42 of the judgment – set out below - that the applicant is not entitled to compensation for the delay in exploiting all forms of the medicinal product he has brought to market but rather for the delay they have experienced in marketing what constitutes the '*core inventive advanc*e' which is this case was the monotherapy based on irbesartan:

> 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

[31] (i) *Biogen, C-181/95,* Biogen Inc. v Smithkline Beecham Biologicals SA; for text of decision see http://curia.europa.eu/juris/showPdf.jsf?text=&docid=100342&pageIndex=0&doclang=en&mode=req&dir=&occ=first&part=1&cid=119455; (ii) *AHP, C-482/07,* AHP Manufacturing BV v Bureau voor de Industriële Eigendom; for text of decision see http://curia.europa.eu/juris/document/document.jsf?text=&docid=73083&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=120932

> 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.

Thus, a second SPC based on the same basic patent would only appear possible in the situation where this second product is innovative in its own right.

Boehringer, C-577/13

107 In *Boehringer*, C-577/13, also a reference for a preliminary ruling from the UK courts[32], the CJEU considered four questions which related to how explicitly the active ingredients in a monotherapy and in a combination therapy for which SPCs had already been granted in the UK had to be identified in the basic patent. They also asked if the existence and use of a national post-grant amendment mechanism to identify the active ingredients in the combination in a more explicit manner had any relevance to the granted SPCs. In developing its answers to the referred questions, the CJEU chose not to deal directly with the detailed questions from the UK court, but instead it considered that the subject matter covered by these questions could be looked at in two parts with the material covered by question 2 and 3 being taken together and that covered by question 1 and 4 also being taken together. It transpired that the answer to the combined subject matter covered by question 2 and 3 meant that there was no need to answer the questions covered by the combined subject matter of questions 1 and 4. In considering the combined subject matter covered by question 2 and 3, the court summarised the question it had to answer in the following manner (see para 25 of the judgment):

> "*By its second and third questions, which it is appropriate to examine together and in the first place, the national court is asking, in essence, whether 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 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****. If that question is answered in the negative, the national court is also seeking to ascertain how the duration of*

[32] Reference for a preliminary ruling from United Kingdom, High Court of Justice (England & Wales), Chancery Division (Patents Court) (United Kingdom), made by decision of 31 October 2013, received at the Court on 14 November 2013.

the 'combination SPC' is to be determined, for the purpose of Article 13(1) of that regulation."

108 The CJEU noted that it was common ground in the national proceedings that:

(i) the combination for which the second SPC had been granted was the combination of telmisartan and HCTZ;

(ii) The earlier granted SPC based on this patent was for the single active ingredient telmisartan;

(iii) telmisartan was the innovative active ingredient of Boehringer's basic patent, and was "*the sole subject-matter of the invention*".

(iv) *Boehringer* had not contributed to the discovery of hydrochlorothiazide (HCTZ), which, at the priority date of the patent, was well known within the public domain, as a diuretic;

(v) The claim in the basic patent which relates to HCTZ does not constitute the subject-matter of the invention.

109 In answering the question it posed itself in relation to the subject matter of questions 2 and 3, the court concluded (see para 39) as follows:

"*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*."

110 In reaching this conclusion, the CJEU made a number of relevant points at paras 27, 28 and 32-38 of the judgment. These paras are reproduced below:

"27. It should be noted, first, that, in accordance with Article 3(a) to (d) of Regulation No 469/2009, an SPC is to be granted if, in the Member State in which the application is made and at the date of that application, the product is protected by a basic patent in force, where the product has not already been the subject of an SPC and a valid authorisation to place the product on the market as a medicinal product has been granted and that marketing authorisation is the first authorisation at the date of that application. In so far as concerns the product, as referred to in Article 3(a) and (b) of Regulation No 469/2009, ***it is apparent from a reading of that provision in conjunction with Article 1(c) of the regulation that an SPC may be granted only if the product is protected as such by the basic patent****.*

28. As regards the question whether or not the products at issue in the main proceedings are protected, the parties to those proceedings do not agree on the correct interpretation to be given to the expression 'as such' in Article 1(c) of Regulation No 469/2009."

The court reviewed briefly the different views expressed by the European commission and those member states that submitted written observations in paras

29-31 in relation to the correct interpretation of '*protected as such*' before going on to analyse the question, and answer it, in its own right, in paras 32-38 which are reproduced below (my emphasis added in bold):

> *32 For the purposes of providing a useful answer to Questions 2 and 3, it should be noted that the expression 'as such', as used in Article 1(c) of Regulation No 469/2009, must be given an autonomous interpretation in the light of the objectives pursued by that regulation and the overall scheme of which that expression forms part.*
>
> *33 It should be recalled in that regard, first, that 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 (see, to that effect, judgments in Actavis Group PTC and Actavis UK, C-443/12, EU:C:2013:833, paragraph 29, and Georgetown University, C-484/12, EU:C:2013:828, paragraph 30).*
>
> *34 Second, it should be noted that, according to recitals 4, 5 and 9 in the preamble to Directive No 469/2009, the SPC is designed to re-establish a sufficient period of effective protection of a basic patent by permitting the holder to enjoy an additional period of exclusivity on the expiry of his patent, which is intended to compensate, at least in part, for the delay to the commercial exploitation of his invention by reason of the time which has elapsed between the date on which the application for that patent was filed and the date on which the first marketing authorisation in the European Union was granted (see, to that effect, judgment in Actavis Group PTC and Actavis UK, C-443/12, EU:C:2013:833, paragraph 31 and the case-law cited).*
>
> *35 However, the Court has also held that the objective pursued by Regulation No 469/2009 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 commercial forms, including in the form of combinations based on the same active ingredient (see, to that effect, judgment in Actavis Group PTC and Actavis UK, EU:C:2013:833, paragraph 40).*
>
> ***36 In the light of the need, referred to, inter alia, in recital 10 in the preamble to Regulation No 469/2009, to take into account all the interests at stake, including those of public health, if it were accepted that all subsequent marketing of an active ingredient in conjunction with an unlimited number of other active ingredients which do not constitute the subject-matter of the invention covered by the basic patent would confer 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 (see, to that effect, judgment in Actavis Group PTC and Actavis UK, EU:C:2013:833, paragraph 41).***
>
> ***37 Accordingly, in view of the interests referred to in recitals 4, 5, 9 and 10 in the preamble to Directive 469/2009, 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, an active ingredient,***

> ***protected as such by the holder's basic patent and constituting the subject-matter of the invention covered by that patent, and, on the other, another substance which does not constitute the subject-matter of the invention covered by the basic patent (see, to that effect, judgment in Actavis Group PTC and Actavis UK, EU:C:2013:833, paragraph 30).***
>
> *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.***

111 Thus, both of these recent CJEU decisions have provided some guidance on determining whether or not one SPC can serve as the basic patent for more than one SPC. These cases have shown the circumstances under which the grant of a second SPC is precluded or incorrect. So a consideration of both decisions should provide some guidance on establishing when the basic patent can serve as the basis for more than one SPC.

112 While it is the case that *Sanofi* and Boehringer use different expressions to determine what the basic patent must protect or cover in order to provide the basis for a valid SPC application, i.e. *Sanofi* refers to "*a patent protecting an innovative active ingredient*" (see para 43) and *Boehringer* states that where "*a basic patent includes a claim to a product comprising an active ingredient which constitutes the sole subject-matter of the invention*" (see para 39), both of these decisions do make clear that the active ingredient for which an SPC is sought must be "*protected as such*" by the patent (see *Boehringer* at paras 38 and 39 and *Sanofi* at para 43). I consider that what both of these decisions make clear is that one has to consider the basic patent to determine what is the '*innovative active ingredient*' that the basic patent covers and, if an applicant is seeking a second SPC based on this basic patent, one has to determine if this SPC application relates to the same or another '*innovative active ingredient*' that constitutes the subject matter of the invention.

Analysis

113 At the hearing Mr Horgan began by reminding me of the importance of the recitals in determining the purpose of the regulation and, in particular, recital 4 which indicates that the purpose of the SPC regulation is to provide recognition of the "insufficient" recompense for the patent holder owing to the regulatory delay to obtain marketing authorisation. While I accept this, I must also take into account recital 10, which requires me to account for the interests of public health systems and not only the effect on the innovator, when considering the purpose of the regulation. *Boehringer* affirms this view (see para 36 cited above).

114 Mr Horgan characterised the objection raised by the examiner as primarily with respect to non-compliance with Article 3(c) but with a link to Article 3(a), i.e. to determine if the product for which the SPC is being applied for is already the subject of an earlier certificate [i.e. Article 3(c)], it is necessary to take account of what protected by the patent means in relation to the grant of any earlier SPC(s) [i.e. Article 3(a)].

115 In considering the situation, such as we have in this case, where the applicant is arguing that the basic patent provides protection for more than one product, it is necessary to take account of recent CJEU case law which indicates what factors to take into account when determining if the basic patent protects the combination of one active ingredient with a second active ingredient when the basic patent has already be used as the basis for one or more earlier granted SPCs involving the same active ingredient, either alone and in a combination with a third active ingredient. Specifically, to grant an SPC in this case, it is necessary to establish that the basic patent protects the combination of ezetimibe and atorvastatin – an Article 3(a) question - and, that none of the earlier granted SPCs based on this patent also, protect this combination – an Article 3(c) question. Thus, Mr Horgan is correct to refer to there being a link between Article 3(c) and Article 3(a), in so far as it is a condition that the combination is protected by the basic patent if it is the subject of an earlier SPC. However, it is only when there is a later SPC application based on the same patent but a later MA seeking to protect the same combination that the application fails under Article 3(c).

116 I note that both the examiner and the agent acting for the applicant, Mr Horgan, have considered the relevance of the *Sanofi* and *Boehringer* cases from the CJEU in some depth. I agree that my consideration of compliance with Article 3(c) should begin with these judgments as they both concern scenarios wherein a first SPC for the active ingredient in the monotherapy product has been followed by an SPC application for a combination product involving the same active ingredient based on the same patent but a subsequent marketing authorisation. In his analysis of these judgments, Mr Horgan started from the premise that it is possible to obtain more than one SPC relying on the same basic patent in the situation, as is quite common, where the basic patent protects more than one product, for example, using a Markush formula. He illustrated this, in particular, by reference to *Sanofi* at paragraph 29; *Boehringer* at paragraph 33 and the earlier CJEU judgment in *Georgetown University v Octrooicentrum Nederland, C 484/12*, hereafter "*Georgetown II*"[33], at paragraph 38. As the latter two references are identical, I quote only the first of these below:

> "*29. In that regard, it is possible, 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." (Sanofi, C-443/12)*

and

> *"33. It should be recalled in that regard, first, that 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*

[33] For full text of CJEU decision see *C-484/12* [2013] ECR or http://curia.europa.eu/juris/document/document.jsf?text=&docid=145524&pageIndex=0&doclang=en&mode=lst&dir=&occ=first&part=1&cid=123577

Article 1(b) and (c) of that regulation." (Boehringer, C-577/13; *Georgetown II, C-484/12)*[34]

I agree that the CJEU does acknowledge that it is possible to grant more than one SPC based on the same basic patent and that it does not preclude the grant of more than one SPC from a single basic patent if that patent protects different products which are, in turn, active ingredients in medicinal products authorised by different MAs.

117 Mr Horgan continued his analysis by reference to *Sanofi*, paragraphs 30, 41 and 42, which state as follows:

> *"30. However, 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.*

and

> *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*

[34] Paragraph 33 of *Boehringer, C-577/13* or paragraph 38 of *Georgetown II, C-484/12.*

> *covered a totally separate innovation, confer entitlement to an SPC for that new combination that is subsequently placed on the market."*

and, also with reference to *Boehringer*, paragraphs 37 and 38:

> *"37. Accordingly, in view of the interests referred to in recitals 4, 5, 9 and 10 in the preamble to Directive 469/2009, 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, an active ingredient, protected as such by the holder's basic patent and constituting the subject-matter of the invention covered by that patent, and, on the other, another substance which does not constitute the subject-matter of the invention covered by the basic patent (see, to that effect, judgment in Actavis Group PTC and Actavis UK, EU:C:2013:833, paragraph 30).*
>
> *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."*

At the hearing Mr Horgan concluded from these passages that "*it is not clear to me that the CJEU here says the core inventive advance must be the test you use*" and "*It is not entirely clear to me whether they are just reciting what the first instance court said or approving of that as a test. I would suggest that they are just mentioning it*" (referring to *Sanofi*, para 30). Mr Horgan instead settled on a different test "*the test of independent validity of the claim. In other words you can grant the SPC where there is a larger gap between the subject matter of a claim to the combination and the prior art than the monotherapy and the prior art*" (see transcript, page 56/57). He characterised this test by reference to the situation in the current applications where the use of combinations of azetidinone compounds in combination with other actives such as statins was not part of the state of the art at the filing/priority date of the application. It was also not well known at this time to use statins in combination with azetidinones or indeed other classes of compounds to reduce cholesterol. Unlike the situation in *Sanofi* and *Boehringer*, where it was well know at the date of the application for the patent to combine compounds such as irbesartan or losartan, examples of what Mr Horgan referred to as the 'sartan' class of compounds, which are Angiotensin II receptor inhibitors - with diuretics, such as HCTZ, to improve treatment of high blood pressure. HCTZ was a well known and well established diuretic at the date that the patents involved in the *Sanofi* and *Boehringer* cases were applied for. Thus, Mr. Horgan argues that there was no innovation involved in combining a sartan with HCTZ, thus the innovative active ingredient 'protected as such' by the patent in both the *Sanofi* and *Boehringer* cases was irbesartan itself. By contrast in the present case, it was not well known in the art when the patent application was made that azetidinones could be combined usefully with statins to treat heart disease by reducing cholesterol in humans. Mr Horgan referred to this contrast at the hearing thus: "*we are saying that the difference here is that there was no argument in [the]* Boehringer *and* Sanofi *cases, that there was some independent validity for that claim* [i.e. the claim relating to the combination of azetidinone and CoEnzymeA synthetase inhibitors such as simvastatin or atorvastatin], *some further distance between the claim and the prior art than there was for the monotherapy alone."* (see transcript, page 60).

118 The examiner develops his objection in reference to *Sanofi* paragraphs 30, 42 and 43. In particular, the second sentence of paragraph 42, i.e.

> *" ..... 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" (Sanofi, C443/12)*

This relies on the view that the present application offends Article 3(c) as it does not rely on, "*a new patent*" or "*totally separate innovation*", as an SPC for the mono-product ezetimibe has already been granted based on EP (UK) 0 720 599, the basic patent of the current application. In addition, an SPC has also been granted for a combination of ezetimibe with a different statin – simvastatin – based on this basic patent already

119 The examiner develops this view by reference to para 38 of *Georgetown II* which states that:

> *"...the wording of Article 3(c) of Regulation 469/2009 itself* ***precludes*** *that holder from obtaining, on the basis of that same patent, another SPC relating to the very same HPV-16 as a 'product' on the basis of a subsequent MA for another medicinal product which also contains HPV-16,* ***unless****, in that other medicinal product, the 'product' that is the subject of the SPC application relates in fact to a different HPV-16 falling within the limits of protection conferred by the basic patent relied upon for the purposes of the application* (see, to that effect *Neurim Pharmaceuticals (1991)*, paragraph 30)"

In *Georgetown II*, it was concluded that the same patent covering the preparation of human papilloma virus-like particles of HPV6, HPV11, HPV16 and/or HPV16, singly or in any combination, could be used as the basis for more than one SPC based on the marketing authorisations for a four HPV component combination vaccine, *Gardisil*, or a two HPV component combination vaccine, *Cervarix*[35]. The examiner considered that this passage refers to a prohibition on combination products where, like the present circumstance, there is an earlier SPC to the active ingredient of the monoproduct and a subsequent combination product based on a different MA but the same basic patent. I disagree. I consider that this passage restates Article 3(c) in relation to SPCs based on marketing authorisations for the monoproduct or combination product. I find this view is supported by the reference in paragraph 37 to the two marketing authorisations which cover HPV-16:

> *"37. However, it would appear from the information provided in the order for reference that the active ingredient protected by the basic patent in respect of which Georgetown University has applied, in the main proceedings, for an SPC*

[35] *Gardisil*, also known as Gardisil or Silgard, is a recombinant human papillomavirus vaccine for use in the prevention of certain strains of human papillomavirus, specifically HPV types 6, 11, 16 and 18. *Cervarix* is a recombinant human papillomavirus vaccine for use in the prevention of certain strains of human papillomavirus, specifically HPV types 16 and 18, that cause about 70% of cervical cancer cases.

on the basis of the MA for Gardasil, namely HPV-16, may also be found in another medicinal product, Cervarix, which was subsequently granted an MA."

Given the context provided by paragraph 37, I am of the view that the court intended the comments of paragraph 38 to concern different monoproducts protected by the same basic patent. Having considered the examiner's view of Georgetown II, I am left to resolve what was meant by the comments in *Sanofi*, paragraph 42. There is merit in the *prima facie* view set out by the examiner, but I believe this interpretation does not have the benefit of the comments in *Boehringer* which issued after the examiner issued his final report.

120 I consider that the court in *Boehringer* does not presuppose that a patent that protects a monoproduct is incapable of protecting "*within the subject matter of the invention*" or its "*core inventive advance*", an additional combination product involving the same active ingredient found in the monoproduct. I find support for this in paragraphs 28-34 of *Boehringer* (see above). The court refers to the observations of some member states and the European Commission in paragraphs 28-32 which specifically concern the interplay of mono- and combination products, before observing, in paras 33 and 34, "*that it is possible in principle, on the basis of a patent that protects several different products, to obtain several SPCs provided inter alia that each of those products is protected 'as such' by the basic patent...*". Given the context of the latter, I find that this supports the proposal that a combination product may be awarded an SPC based on a patent that also protects the monoproduct. I am satisfied that I can resolve the meaning of paragraph 42 of *Sanofi* in the context provided by *Boehringer* because this paragraph of *Sanofi* concerns the situation wherein the basic patent does not protect another active ingredient '*as such'*.

121 Turning to my analysis of Mr Horgan's arguments, I consider that the doubt he expressed concerning the '*core inventive advance'* test (see above) is misplaced, I am of the view that the court's approval of the core inventive advance test is brought out in paragraph 41 of *Sanofi* wherein the CJEU references the test in the context of the objective of the Regulation. Nonetheless the court in *Boehringer* did not state that it applied the same test. Thus I will reserve judgment on Mr Horgan's proposed test until I determine if there is a test I can arrive at from *Sanofi* and *Boehringer*.

122 I will continue to consider *Boehringer* to determine if it suggests any other reason I should find Article 3(c) is not complied with, and consider if it proposes a test I can apply. If a test is to be found in *Boehringer*, it is, in my view, formulated in paragraphs 38 & 39 of the judgment (see above). In the situation where the basic patent covers an active ingredient as a monotherapy which is the subject of an MA and SPC and a combination of this active ingredient with one or more active ingredients which is the subject of a later MA, a second SPC cannot be granted to the combination in the situation where the following applies: (a) the basic patent has a claim to the product comprising the active ingredient which constitutes the sole subject-matter of the invention, for which the holder of the patent has already obtained an SPC; (b) the basic patent also includes a subsequent claim to a product comprising a combination of the active ingredient which constitutes the sole subject-matter of the invention and at least one other substance that does not constitute the subject matter of the invention.

123 In *Boehringer* the court determined that the '*sole subject matter*' of the invention was the monoproduct. Given that the court determined (in paragraph 41) that an SPC should not have been granted "*irrespective of whether a new claim to hydrochlorothiazide was added to the basic patent after it had been granted*", I consider this shows that the test requires more than merely the inclusion of a claim in the basic patent identifying the combination, as such a test would have allowed the grant of an SPC to the combination product (which was rejected by the CJEU).

124 I find the test in *Boehringer* is not substantively different from that in *Sanofi,* the subject matter of the invention is a different way of stating the core inventive advance, the test in *Boehringer* is merely developed from *Sanofi* with the benefit of clarifying what may constitute a product "as such". I find support that the CJEU intended the tests to have the same meaning from the fact that in *Boehringer* paragraph 37 (see above), it refers directly to para 30 of *Sanofi*. I consider that *Boehringer* advances the situation from *Sanofi* to require that the product which is the subject of the SPC application is 'protected as such'.

125 To determine if the combination is protected as such by the basic patent, I will turn to what was known at the time of the priority date of the basic patent in the art of drug combinations to treat hypercholesterolaemia, and what the patent teaches. I have been addressed on this in a witness statement by Professor Gerd Assman which (in his own words) "*addresses the treatment of coronary heart disease with lipid lowering agents in the early 1990's in addition to the relative efficacy and clinical benefits of ezetimibe monotherapies and ezetimibe/statin combination therapies.*" He points out that "*To achieve the desirable low target values of LDL cholesterol not infrequently requires the highest approved dose of a statin at which unwanted side effects are more common*." At the priority date, the existing combinations (as indicated in paragraph [0008] of the basic patent were limited to treating patients with severe hypercholesterolemia for whom nothing else worked, they suffered from the combined side effects and contraindications of each of the individual drugs in the combination and there was no suggestion that the combination of the present SPC (i.e., an azetidinone - ezetimibe - and a statin - atorvastatin) would be useful. At the priority date of the combination (which I have checked is 9 June 1994), Professor Assman did not find the combination of the SPC application was known and found that the combination represented a significant technical advance "*The introduction of ezetimibe in combination with statins was a notable further improvement to the known available treatments of [sic] therapies. Particularly where (i) the ezetimibe plus statin combination therapy contained a statin in a low dosage (producing comparable cholesterol lowering but with reduced side effects); or (ii) the combination therapy contained a statin in an equivalent dosage to monotherapy and achieved greater cholesterol lowering and fewer cardiovascular events. Although combination therapy is something that had been desired to achieve maximum lowering of LDL cholesterol, it was not possible before the advent of ezetimibe"* (see para 42 of witness statement).

126 Taking account of Professor Assman's explanation of the development of the combination of azetidinones with statins as a therapy to reduce cholesterol, I am satisfied that ezetimibe in combination with atorvastatin was an innovative product at the priority date of the application. At this date, ezetimibe in combination with atorvastatin was novel and inventive. This combination could <u>not</u> be considered to

involve a component that was well known in the art at the priority date for achieving a relevant therapeutic effect, in the same way that HCTZ was found to be in *Sanofi* and *Boehringer*. I am satisfied that the combination is '*protected as such*' by the basic patent. At the hearing, Mr Horgan directed me to consider the basic patent, especially paras [0015], [0016] and [0017] which refer to combinations and methods of treatment; para [0028] which refers to the role of HMG CoA reductase inhibitors in general and identifies some specific inhibitors, including CI-981 (atorvastatin); and paras [0066]-[0068] which refers to dosage amounts of the combinations and their use in combination or separate sequential administration, as well as claims 1, 16 and 17. I have considered these disclosures and reviewed the basic patent in full and I find that the combination product is part of the subject matter of the invention, is protected by claims 16 and 17 and is supported by the description. The patent is directed to azetidinones and their use as mono-products and in combination with a cholesterol biosynthesis inhibitor to treat atherosclerosis. Although the specific combination of the SPC application is not listed as an example in the patent, it is considered to be supported, not least by the specific dosage regimes that encompass the present combination found in para [0066] of the patent as filed, as well as the named examples of HMG CoA reductase inhibitors referred to in para [0028].

127 I consider that the above mentioned disclosure in the basic patent makes this situation different to that in *Boehringer* and *Sanofi* where the court concluded that the requirement to be '*protected as such'* was not fulfilled by inclusion of a claim to the combination. Something more is required in terms of identifying how the combination product which is the subject of the later MA and SPC application relates to the subject matter of the patent. Having formulated what I consider is a workable approach; I am not minded to adopt the test suggested by Mr Horgan, not least because there is no clear basis for it in the CJEU judgments discussed above.

128 Accordingly I am satisfied that the combination of ezetimibe and atorvastatin is protected as such by the basic patent and that the monotherapy is not the sole subject matter of the invention. The combination of the present application involves the active ingredient, ezetimibe, the subject of an earlier granted SPC, with atorvastatin and I consider this combination is part of the subject matter or innovation protected by the patent and represents the core inventive advance disclosed in the basic patent – the preparation and use of azetidinones, such as ezetimibe, both alone and in combination with a cholesterol biosynthesis inhibitor, to reduce cholesterol levels and treat atherosclerosis. Thus, I am satisfied that the present application meets the requirement of Article 3(c) of the SPC regulation.

Conclusion

129 Taking account of all of the above, I find that in relation to the present application for supplementary protection certificate SPC/GB14/062, for the combination product "*Ezetimibe and atorvastatin or pharmaceutically acceptable salts thereof, including atorvastatin as atorvastatin calcium trihydrate*", the application as filed does not meet the requirement of Article 3(b) of the SPC regulation. At the date of application, the applicant did not have a valid authorisation granted in accordance with Directive 2001/83/EC to the place the medicinal product comprising this combination on the

market in the UK. A valid marketing authorisation for the medicinal product comprising this combination was issued by the relevant competent authority in the UK on 10 October 2015 within the 30 day period for doing so set down under Directive 2001/83/EC. The date of application for the SPC was 12 September 2015 and the basic patent expired on 13 September 2015. On the date of application for the SPC, a valid marketing authorisation for the medicinal product ATOZET had not been granted in the UK.

130 In case I am in error in my conclusion in relation to Article 3(b), I have considered if the application for this combination product also meets the requirement of Article 3(c) of the SPC Regulation that the product for which an SPC is sought must not already have been the subject of a certificate. I consider that the combination of ezetimibe and atorvastatin is '*protected as such*' by the basic patent. It is part of the subject matter or innovation protected by the patent and falls within the core inventive advance disclosed in the basic patent. Thus, I am satisfied that the present application meets the requirement of Article 3(c) of the SPC regulation.

Appeal

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

Dr L Cullen
Deputy Director, acting for the Comptroller

Glossary of abbreviations used in this decision

BfArM	*Bundesinstitut für Arzneimittel und Medizinprodukte* [the German Medicines Agency – equivalent of MHRA in UK]
CJEU	Court of Justice of the European Union
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures – Human
CMS	Concerned Member State
DCP	DeCentralised Procedure (for authorisation of medicinal products)
EU	European Union
EMA	European Medicines Agency
HCTZ	Hydrochlorothiazide
HMA	Heads of Medicines Agencies
NCA	National Competent Authority
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Authority
MRP	Mutual Recognition Procedure (for authorisation of medicinal products)
MS	Member State (of the European Union)
MSD	Merck, Sharp & Dohme
PIL	Product Information Leaflet
PL	Package Label
RMS	Reference Member State
RTM	Registered Trade Mark
SPC	Supplementary Protection Certificate
SmPC	Summary of Product Characteristics

Annex 1

Flow Chart of the Decentralised Procedure DCP[1]

Pre-procedural Step	
Before Day -14	Applicant discussions with RMS RMS allocates procedure number. Creation in CTS.
Day –14	Submission of the dossier to the RMS and CMSs Validation of the application –.
Assessment step I	
Day 0	RMS starts the procedure
Day 70	RMS forwards the Preliminary Assessment Report (PrAR),SPC , PL and labelling to the CMSs
Until Day 100	CMSs send their comments to the RMS
Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.
Clock-off period	Applicant may send draft responses to the RMS and agrees the date with the RMS for submission of the final response. Applicant sends the final response document to the RMS and CMSs within a recommended period of 3 months, which could be extended if justified
Day 106	Valid submission of the response of the applicant received. RMS restarts the procedure.
Day 106 - 120	RMS updates PrAR to prepare Draft Assessment Report (DAR) draft SPC, draft labelling and draft PIL to CMSs.
Day 120	RMS may close procedure if consensus reached. Proceed to national 30 days step for granting MA.
Assessment step II	
Day 120 (Day 0)	If consensus not reached RMS sends the DAR, draft SPC, draft labelling and draft PIL to CMSs
Day 145 (Day 25)	CMSs sends final comments to RMS
Day 150 (Day 30)	RMS may close procedure if consensus reached. Proceed to national 30 days step for granting MA
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification and prepare a short report for discussion at Coordination Group
Until Day 205 (Day85)	Breakout Group of involved Member States reaches consensus on the matter
Day 210 (Day 90)	Closure of the procedure including CMSs approval of assessment report, SPC, labelling and PIL, or referral to Co-ordination group. Proceed to national 30 days step for granting MA.
Day 210 (at the latest)	If consensus was not reached at day 210, points of disagreement will be referred to the Co-ordination group for resolution
Day 270 (at the latest)	Final position adopted by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement
National step	
Day 110/125/155/215/275	Applicant sends high quality national translations of SPC, labelling and PIL to CMS and RMS
Day 135/150/180/240	Granting of national marketing authorisation in RMS and CMSs if no referral to the Co-ordination group. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).
Day 300	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the Co-ordination group and no referral to the CHMP/CVMP. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).

[1] Taken from February 2007 edition of Chapter 2: *Mutual Recognition*, of Volume 2A: *Procedures for Marketing Authorisation*, in Volume 2: *the Notice to Applicants* (see Annex II, page 38) of "*The Rules governing Medicinal Products in the European Union*" - see http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap2_2007-02_en.pdf.