Intellectual Property Office

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19 December 2014

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

APPLICANT	Icahn School of Medicine at Mount Sinai
ISSUE	Whether application SPC/GB13/069 for a supplementary protection certificate meets the requirements of Article 3(a) of the Regulation
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 This decision relates to supplementary protection certificate (SPC) application SPC/GB13/069 in the name of Icahn School of Medicine at Mount Sinai ("the applicant"), filed on 25 November 2013. The product for which an SPC is sought, as listed on Patents Form SP1 filed with this application, is *Agalsidase-beta*, a glycosylated human α-Galactosidase A enzyme which is the active ingredient in the medicinal product marketed by a third party (Genzyme Corporation) under the name *Fabrazyme* (RTM)[1].

2 The basic patent upon which the SPC application relies is EP(UK) 2210947B1, entitled '*Method for producing secreted proteins'*, which was filed on 30 November 1993. The basic patent expired on 29 November 2013. The patent describes methods for producing secreted human α-Galactosidase A enzyme in Chinese hamster ovary (CHO) cells.

3 The European marketing authorisation (MA) EU/1/01/188/001, granted by the European Commission on 7 August 2001 for the medicinal product *Fabrazyme* to Genzyme B.V with an address in the Netherlands, was supplied in support of the SPC application.

4 This application has been the subject of an extensive round of correspondence between the applicant and their agent, Powell Gilbert LLP, and the examiner. The examiner issued official examination reports dated 4 December 2013, 17 June 2014

[1] Fabrazyme is a Registered Trade Mark in the UK.

and 30 September 2014 referring to substantive issues concerning this SPC application. In addition, the examiner sent letters to the applicant providing copies of third party observations filed in relation to this application dated 28 January 2014, 12 March 2014, 19 March 2014, 10 June 2014 and 25 September 2014. The applicant requested that the application be referred for consideration by a senior officer at an oral hearing in their letter dated 18 July 2014.

5 Following the submission of the applicant's skeleton argument on 8 October 2014, a final set of third party observations was received (commenting on the applicant's skeleton argument) and these were copied to the applicant with the examiner's official letter of 14 October 2014.

6 Having considered the arguments presented in the applicant's skeleton argument about how to identify the product claimed in claim 1 of the basic patent as *agalsidase-beta*, the applicant was asked, in the official letter dated 13 October 2014, to also address the hearing officer on how this application meets the requirements of Article 3(c) of the Regulation in light of the existing granted SPC for the product '*agalsidase-alfa'* (marketed as the medicinal product Replagal (RTM)[2]), an α-Galactosidase A enzyme produced in human cells (as distinct from CHO cells).

7 The case came before me at an oral hearing held in Newport on 15 October 2014. Dr Philip Mountjoy was in attendance as hearing assistant, together with the examiner, Dr Jason Bellia. The applicant was represented at the hearing by Miss Charlotte May Q.C., instructed by Dr Penny Gilbert and Dr David Lancaster on behalf of Powell Gilbert LLP (the recorded agents for the SPC application). In addition, Professor Robert Desnick and Professor Yiannis Ioannou (both named inventors on the basic patent EP(UK) 2210947 B1), Dr Sybil Lombillo (in-house counsel at Icahn School of Medicine at Mount Sinai, New York, USA), and Mr Thomas Meloro (Wilkie Farr & Gallagher, external US counsel for Mount Sinai) also attended the hearing on behalf of the applicant.

Technical background

8 I was addressed in some detail at the hearing about the technology to which the present application relates. I believe that this technical background is pertinent to the issues to be decided for this SPC application, and as such I will provide a summary of it here.

9 α-Galactosidase A is an enzyme which breaks down a certain type of glycolipid within a compartment of the cell called a lysosome. Patients suffering from a disease called Fabry Disease have a deficiency in this enzyme, and consequently these patients cannot break down the aforementioned glycolipid. This can lead to renal, cardiovascular and cerebro-vascular complications.

10 The enzyme itself is glycosylated, which means that the enzyme has a number of different types of sugar components attached to its protein sequence in a step-wise manner once it has been expressed in a cell. The sugars may also be removed or

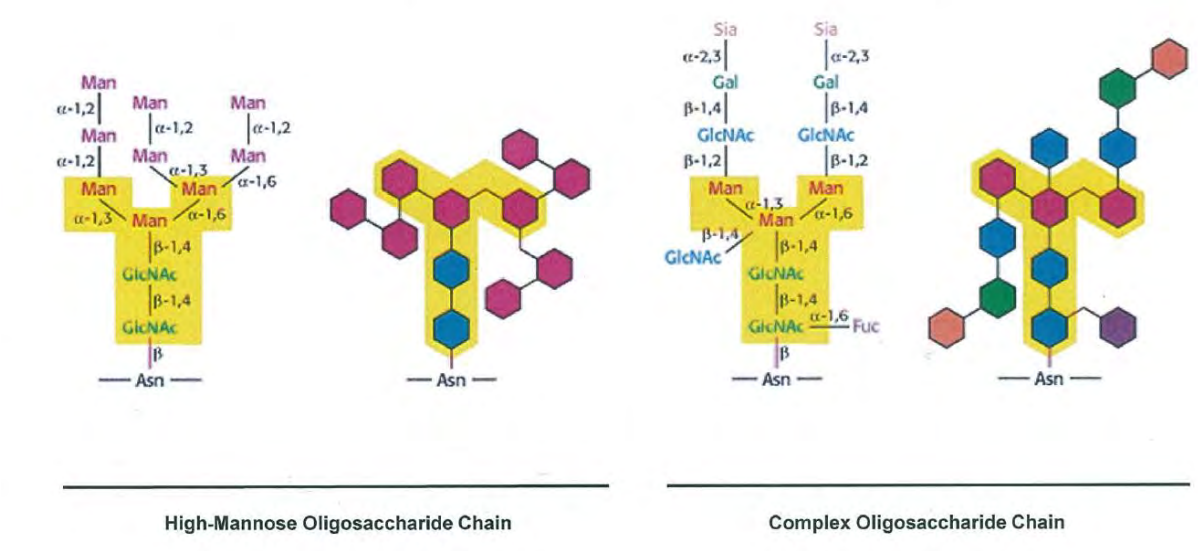
[2] Replagal is a Registered Trade Mark in the UK.

modified during subsequent processing as the enzyme moves through the cell. α-Galactosidase A has three specific glycosylation sites where the sugars can be attached, and chains of sugars are ultimately formed at each site (α-Galactosidase A forms a dimer, which means that there are six glycosylation sites in total).

11 Although the sugars are always attached to α-Galactosidase A at the same three sites on the polypeptide chain, the exact pattern or order of the sugars at each site can vary. One reason for this variation is that multiple different types of sugars can be added in different orders to form the sugar chains on the α-Galactosidase A. The exact order of the sugars can vary, depending on where the α-Galactosidase A is within the cell's processing machinery. Consequently, the α-Galactosidase A enzyme actually exists as a collection of different 'glycoforms' (i.e. forms of the enzyme which differ in the pattern or type of the sugars attached), rather than as a single specific glycoform. This variation arises both when the enzyme is produced in different types of cell lines, and in different batches of the enzyme from the same type of cell line. The sworn declaration from Professor Platt, University of Oxford, which was filed in advance of the hearing, confirms the existence of the aforementioned variation.

12 I was provided with a diagram during the hearing which summarises how the different sugar units can be connected together in the polysaccharide chains which are attached to α-Galactosidase A. I have reproduced this diagram below (see Figure 1 where different sugars are represented by different coloured hexagons). Applying the aforementioned discussion about variation to the example provided in the figure, the different coloured sugar units can be added in different orders or patterns to provide variation in the glycosylation of α-Galactosidase A.

Figure 1. *Glycosylation of α-Galactosidase A*



Glycosylation of α Galactosidase A – Adapted from Berg JM, Tymoczko JL & Stryer L, Biochemistry, 5th edition, New York: WH Freeman (2002), Section 11.3.

13 Different types of sugars are added to the α-Galactosidase A by a number of different enzymes. For example, α-2,6-sialyltransferase adds sialic acid (a type of

sugar unit) in the 2,6 conformation. In contrast, α-2,3-sialyltransferase adds sialic acid in the 2,3 conformation.

14 An important point to consider in relation to the present application is that different types of cells have different complements of enzymes for adding the sugars to the α-Galactosidase A enzyme. Consequently, the glycosylation pattern of α-Galactosidase A is also dependent on the particular type of cell which is being used to express the enzyme. For example, human cells have α-2,6-sialyltransferase, whereas CHO cells lack this enzyme. Furthermore, CHO cells will produce glycosylation patterns with a particular level of mannose-6-phosphate within a characteristic range, whereas human cells produce a different level of mannose-6-phosphate within a characteristic range specific for human cells.

15 A particular cell type (e.g., a CHO cell) will produce α-Galactosidase A with a consistent level of sialylation and mannose-6-phosphate within a defined range. However, the particular range observed will vary from one cell type to another. For example, CHO cells will have a different characteristic range to human cells. Consequently, a population of glycoforms of α-Galactosidase A is produced with a consistent overall profile of these sugars in each cell type, but there can be variation in the order of the sugars in a particular sugar chain, as discussed above. I was informed at the hearing that a normal distribution of glycosylation patterns is effectively produced for α-Galactosidase A, but that the normal distribution is different in different cell types. I believe that this is a convenient way of visualising the concept of the range of glycosylation patterns which can be produced for α-Galactosidase A.

16 The mannose-6-phosphate on the α-Galactosidase A is important for targeting the enzyme to the right location within the cell to allow the enzyme to carry out its function of breaking down glycolipids. Mannose-6-phosphate receptors on cells bind to the mannose-6-phosphate on the α-Galactosidase A enzyme to cause the enzyme to be taken up into the cell, and to cause it to be transported to the correct location in the cell. However, the particular position of the mannose-6-phosphate in the sugar chains attached to α-Galactosidase A is not important. It is the overall level of the mannose-6-phosphate on the α-Galactosidase A which is the key factor for controlling the uptake of the enzyme.

17 Sialic acid on the α-Galactosidase A affects the bioavailability of the enzyme by controlling clearance of the enzyme by the liver. Sialic acid prevents the α-Galactosidase A enzyme from being taken up and removed by the liver.

18 The relative proportions of mannose-6-phosphate and sialic acid are therefore important to ensure that the α-Galactosidase A is not removed from the body by the liver before it can be taken up by cells to carry out its enzymatic function.

Third party observations on SPC applications

19 As briefly noted above, several sets of third party observations have been filed in relation to this case. Before dealing with the issue to be decided and the relevance, if any, of these third party observations to this issue, I will first consider the basis, if

any, for making such observations and for taking such observations into account in relation to an application for an SPC.

20 I have briefly summarised the relevant parts of the prosecution history of this case below in so far as it is relevant to placing these third party observations into context.

21 The examiner's first official examination report on this SPC application was issued on 4 December 2013. The report identified a number of substantive issues in relation to the application, including compliance with Article 3(a) of Council Regulation (EEC) No 469/2009 concerning the creation of a supplementary protection certificate for medicinal products (hereafter "the SPC Regulation")[3].

22 On 2 May 2014, the applicant's agent provided a response to the first examination report.

23 Observations on this SPC application were received from a third party on 22 January 2014, on 10 March 2014 and on 9 June 2014. In each case these observations were filed on behalf of the same third party - Genzyme Corporation. I note that the holder of the marketing authorisation provided by the applicant in support of this SPC application is one of the entities in the Genzyme group of companies, Genzyme B.V. with an address in the Netherlands. The examiner issued letters to the applicant dated 28 January 2014, 12 March 2014, 19 March 2014, and 10 June 2014, providing copies of the observations from the third party filed in relation to their application. The examiner notified the applicant in these letters that he would consider these observations as part of the preparation of his next official examination report.

24 In his second examination report dated 17 June 2014, the examiner considered that a number of substantive issues, including compliance with Article 3(a), were still at issue in relation to this application. The examiner referred to the content of the third party observations when maintaining his objection that the application did not meet the requirements of Article 3(a) of the Regulation.

25 The applicant's agent replied to this second official examination report in their letter of 18 July 2014 providing various counter-arguments and supporting documents as to why the application does meet the requirements of Article 3(a) of the SPC Regulation. The applicant also requested that the application be referred for determination by a senior officer.

26 In response to this request, an oral hearing was scheduled for 15 October 2014 and the applicant was notified by the Office of this date by letter dated 28 August 2014. Further observations were received from the same third party in a letter dated 23 September 2014. The examiner issued a further letter dated 25 September 2014 providing the applicant with copies of these further observations and, he subsequently referred to these third party observations in his letter to the applicant summarising the issues that were at issue for the hearing dated 30 September 2014.Following the submission of the applicant's skeleton argument on 8 October 2014 in advance of the hearing, a final set of observations from Genzyme

[3] Council Regulation (EC) 469/2009 concerning the creation of a supplementary protection certificate for medicinal products (codified version).

Corporation was received. These observations commented on the skeleton argument filed by the applicant and were copied to the applicant in an official letter from the examiner dated 14 October 2014.

Section 21 of the Patents Act

27 Section 21 of the Patents Act 1977 (hereinafter the Act) entitled '*Observations by third party on patentability*' provides as follows:

> *"Where an application for a patent has been published but a patent has not yet been granted, any person may make observations in writing to the comptroller on the question of whether the invention is a patentable invention, stating reasons for the observations, and the comptroller shall consider the observations in accordance with rules*
>
> *It is hereby declared that a person does not become a party to any proceedings under this Act before the comptroller by reason only that he makes observations under this Section."*

28 Section 128B of the Act states that Schedule 4A to the Act contains provisions about the application of the Act in relation to supplementary protection certificates. Section 21 applies to applications for supplementary protection certificates, and as this section indicates, such observations can be filed at any time before the grant of an SPC.

29 Consequently, I am satisfied that the observations filed by the third party in relation to the present SPC application are appropriate and that they have been dealt with in an appropriate manner, and that the examiner was correct to take the observations into account when considering whether the current application met the requirements of the SPC Regulation.

30 As indicated in Section 21 of the Patents Act, the third party (in this case Genzyme Corporation) did not become a party to the present *ex parte* proceedings between the comptroller and the applicant Icahn School of Medicine at Mount Sinai concerning this SPC application.

The Basic Patent

31 The basic patent EP(UK) 2210947 B1 filed in support of the present application contains a single claim to a method for producing secreted human α-Galactosidase A as set out below:

1. A method for producing a secreted human α-Galactosidase A, comprising:

a) amplifying an α-Galactosidase A nucleotide sequence in an engineered CHO cell expressing α-Galactosidase A and dihydrofolate reductase (DHFR);
b) culturing said cell under conditions in which the α-Galactosidase A is overexpressed resulting in the formation of crystalline structures containing α-Galactosidase A in membrane limited vesicles, and wherein said α-Galactosidase A is secreted into the cell culture medium; and
c) Isolating said α-Galactosidase A from the cell culture medium,

wherein said α-Galactosidase A contains mannose-6-phosphate, and wherein the cell is obtainable by step-wise growth in increasing methotrexate concentrations up to 1000 μM.

The Relevant Law

The SPC Regulation

32 Article 1 of Council Regulation (EC) 469/2009 concerning the creation of a supplementary protection certificate for medicinal products, referred to as the SPC Regulation, provides the following definitions of '*medicinal product'*, '*product*', and '*basic patent*' (emphasis added):

> *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;*
>
> *(c) '**basic patent'** means a patent which protects a product as such, **a process to obtain a product** or an application of a product, and which is designated by its holder for the purpose of the procedure for grant of a certificate.*
>
> *(d) ....*
>
> *(e) ....*

33 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**.*

34 Article 3 of the SPC Regulation defines the conditions for obtaining a certificate (emphasis added) 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) 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) the product has not already been the subject of a certificate;

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

Relevant Case Law

Court of Justice of the European Union (CJEU)

35 There have been a number of recent decisions from the CJEU that deal with the question of what is protected by the basic patent for the purposes of meeting the requirement of Article 3(a) of the SPC regulation. In C-322/10 (*Medeva v Comptroller-General of Patents, hereafter Medeva*), the Court of Justice of the European Union (CJEU) ruled that, for the purposes of Article 3(a) of the SPC Regulation, the product which is the subject of an application for an SPC must be "*specified*" in the wording of the claims of the basic patent filed in support of the application in order for the product to meet the requirement of being protected by a basic patent in force[4].

36 In C-630/10 (*University of Queensland, CSL Ltd v Comptroller-General of Patents, Designs and Trade Marks, hereafter Queensland)*[5] the CJEU provided a decision by reasoned order with reference to C-322/10 (*Medeva*) and a closely related decision, C-422/10 (*Georgetown University, University of Rochester, Loyola University of Chicago v Comptroller-General of Patents, Designs and Trade Marks, hereafter Georgetown*)[6]. In C-630/10 *Queensland*, the CJEU discussed the conditions for grant of an SPC and clarified that if a basic patent relates to a process by which a product is obtained, Article 3(a) only allows an SPC to be granted for a product which is identified in the wording of the claims of the patent as the product deriving from the process in question[7].

37 The CJEU's decisions in C-322/10 *Medeva,* C-422/10 *Georgetown* and C-630/10 *Queensland* all made clear that the conditions for the grant of an SPC under Article 3 are distinct from the protection conferred by a certificate under Article 5 of the Regulation. As such, Article 3 is relevant to the determination of whether an application meets the requirements for the grant of an SPC, whereas Article 5 determines the scope of protection provided by the granted certificate. These decisions also made it clear that the CJEU had rejected the use of the so-called "infringement test" for interpreting what is protected by the patent for the purposes of Article 3(a) of the regulation.

[4] C-322/10 (*Medeva Inc v Comptroller-General of Patents, Designs and Trade Marks*).
[5] C-630/10, *University of Queensland, CSL Ltd v Comptroller-General of Patents, Designs and Trade Marks,* see especially paragraphs 40 and 41.
[6] C-422/10 *(Georgetown University, University of Rochester, Loyola University of Chicago v Comptroller-General of Patents, Designs and Trade Marks)*.

38 In C-630/10 *Queensland*, the CJEU also stated that the grant of an SPC is not conditional on whether it is possible to obtain a product directly as a result of the process by which the product is obtained, where the process has been the subject of a patent. It went on to emphasise this point by stating that whether it is possible to obtain the product directly as a result of the process is irrelevant.

39 The court was asked specifically to address the issue of whether the product (i.e., the active ingredient) which was the subject of the SPC had to be obtained directly by means of the process claimed in the patent – see Question 6 in the reference from the UK High Court which asked:

> *"Q6 In a case like the present one involving a basic patent with claims to "a process to obtain a product" in the sense of Article 1(c) [of Regulation No 469/2009], does the "product" of Article 3(a) [of the Regulation] have to be obtained directly by means of that process?*

The CJEU answered this question, and the others referred, in a reasoned order which followed on from what the CJEU had already said in its earlier judgments in C-322/10 *Medeva*, and C-422/10 *Georgetown*, (mentioned above). The complete answer provided to referred question 6 is as follows (see paragraphs 37-41 of the reasoned order, emphasis added):

> *"Question 6*
>
> *37 By Question 6, the referring court asks whether, in a case involving a basic patent relating to a process by which a product is obtained, it is necessary for the purpose of granting a SPC, in the light in particular of Article 1(c) of Regulation No 469/2009, for it to be possible for the 'product' to be obtained directly by means of that process.*
>
> *38* ***It is sufficient to point out that a patent protecting the process by which a 'product' within the meaning of Regulation No 469/2009 is obtained may, in accordance with Article 2 of the regulation, enable a SPC to be granted and, in that case, in accordance with Article 5 of the regulation, the SPC confers the same rights as conferred by the basic patent as regards the process by which the product is obtained*** **(see Medeva, paragraph 32).**
>
> *39 If the law applicable to such a patent so provides, a SPC granted on the basis of that patent will also extend the protection of the process by which the product is obtained to the product thus obtained* (see, to that effect, Medeva, paragraph 32).
>
> ***40 However, just as Article 3(a) of Regulation No 469/2009 precludes the grant of a SPC relating to active ingredients which are not specified in the wording of the claims of the basic patent*** **(Medeva, paragraph 25),** ***where the basic patent relied on in support of a SPC application relates to the process by which a product is obtained, that provision also precludes a SPC being granted for a product other than that identified in the wording of the claims of that patent as the product deriving from that process. The grant of a SPC is not conditional on whether it is possible to obtain a product directly as a result of the process by which the product is obtained, where that process has been the subject of a patent.***

> ***41 The answer to Question 6 is therefore that, in the case of a basic patent relating to a process by which a product is obtained, Article 3(a) of Regulation No 469/2009 precludes a SPC being granted for a product other than that identified in the wording of the claims of that patent as the product deriving from the process in question. Whether it is possible to obtain the product directly as a result of that process is irrelevant in that regard."***

40 I consider the terms "*specified in the wording of the claims*" and "*identified in the wording of the claims*" as used by the CJEU in the aforementioned series of decisions are equivalent to each other and have the same meaning in terms of describing what is characterised by the wording of the claims.

41 The CJEU has since clarified what it meant by the term '*specified in the wording of the claims*' in C-493/12 (*Eli Lilly & Company v Human Genome Science Inc.,* hereafter *Eli Lilly*)[8]. The court confirmed that a functional definition may suffice for the product to be protected by a basic patent if the claims relate *"...implicitly, but necessarily and specifically, to the active ingredient in question..."*.

UK Courts

42 In *Novartis Pharmaceuticals UK Limited and Medimmune Limited/Medical Research Council*[9] (hereafter *Novartis)*, Arnold J applied the decisions from C-322/10 *Medeva* and C-630/10 *Queensland* to determine that a claim to a general method of producing a molecule with binding specificity for a particular target did not adequately specify or identify the specific antibody ranibizumab for the purposes of meeting the requirements of Article 3(a) of the SPC Regulation.

Issue to be decided

43 The issue to be decided in respect of the present SPC application is whether or not the application meets the requirements of Article 3(a) of the SPC Regulation.

Views of the applicant and the examiner

44 I will first provide a summary of the main points made in arguments presented by the applicant and the examiner, before presenting my analysis and conclusions regarding the issues to be decided.

The Applicant's view

[8] see *paragraphs 39 and 44 of the judgment, and the CJEU's answer to the question referred.*
[9] *Novartis Pharmaceuticals UK Limited and Medimmune Limited/Medical Research Council* [2012] EWHC 181 (Pat).

45 The applicant's skeleton argument provides a summary of their view. The applicant is of the opinion that their SPC application meets the requirements of Article 3(a) of the Regulation as the wording of the claim of EP(UK) 2210947 B1 specifies the product which is the subject of the SPC application. The applicant argues that this is sufficient to satisfy Article 3(a) in light of the CJEU's decision in C-630/10 *Queensland.*

46 If I conclude that the applicant's interpretation of C-630/10 *Queensland* is incorrect, and, if in doing so, I determine that this decision requires that the process claimed in the patent should be capable of making the product which is the subject of the SPC application, the applicant argues that it is indeed possible for the method claimed in EP(UK) 2210947 B1 to make the product agalsidase-beta.

47 The applicant also goes on to argue that the product which is the subject of the marketing authorisation filed in support of their SPC application is, in any case, actually made by the method of the claim of EP(UK) 2210947 B1.

The Examiner's view

48 The examiner's view is summarised in his examination report dated 17 June 2014, and in his additional report dated 30 September 2014.

49 After considering the CJEU's decisions in C-630/10 *Queensland* and C-493/12 (*Eli Lilly*), the examiner is of the opinion that, in order to determine whether the SPC application meets the requirements of Article 3(a) of the Regulation, it must be determined that the product for which an SPC is sought is identified in the wording of the claims of the basic patent as the product deriving from the process in question. In addition, the examiner was also of the opinion that it must be confirmed whether the method of the claim of the basic patent will result in the product agalsidase-beta (the active ingredient of *Fabrazyme*), but not necessarily that the method actually used in the manufacture of *Fabrazyme* is within the scope of the claim of the basic patent.

50 After construing the scope of the claim of the basic patent, the examiner concluded that the claimed method requires the use of CHO cells which have been exposed to stepwise addition of methotrexate (MTX) up to [and including] 1000 µM, or a cell which is identical to a cell produced in this way, and that crystalline structures are subsequently formed in the claimed method.

51 The examiner considered information in the journal article K Lee *et al*., 2003[10]; the information provided in the sworn declarations from Dr Ioannou and Dr Mattaliano; and the information provided in a letter of 2 June 2008 filed at the EPO in respect of patent EP1020528 (the parent patent of the basic patent filed in support of the present SPC application, EP(UK) 2210947 B1). The latter two documents were included in the third party observations filed in relation to the present SPC application.

[10] Glycobiology, Vol. 13, No. 4, 2003, K Lee, et al., 'A biochemical and pharmacological comparison of enzyme replacement therapies for the glycolipid storage disorder Fabry disease', pages 305-313

52 In light of this information, the examiner concluded that CHO cells were exposed to a lower concentration of MTX during the manufacture of *Fabrazyme* than in the claimed method, and that there was no evidence for the formation of crystalline structures at this lower MTX concentration. He also concluded that the feature of culturing cells up to 1000 µM MTX is important to the construction of the claimed method. Consequently, the examiner concluded that the product which forms the subject of the present SPC application was not protected by the basic patent for the purposes of Article 3(a).

Analysis

53 It is clear from Article 1(c) of the Regulation that a basic patent which protects a process to obtain a product, such as the basic patent EP(UK) 2210947 B1 provided in support of the present application, can be used in support of an SPC application.

54 During the hearing, Counsel for the applicant addressed me on three aspects – firstly, their interpretation of C-630/10 *Queensland* and its relevance to the current application; secondly, on the applicant's assertion that *agalsidase-beta* could be produced by the method claimed in the basic patent, and, thirdly, on their assertion that *Fabrazyme* is in fact produced by the process claimed in the basic patent.

55 Counsel instructed me that the latter two assertions were their 'fall back' arguments, which only require consideration if I do not agree with their interpretation of the CJEU's decision in C-630/10 *Queensland* and its relevance for the grant of the present application in suit.

56 I agree with Counsel that the issue of whether the product *agalsidase-beta* could be, or indeed is, produced by the method claimed in the basic patent is only relevant if I do not agree with the applicant's interpretation of C-630/10 *Queensland*. I will therefore start my analysis by considering the CJEU's decision in C-630/10 *Queensland*, before moving on to consider the other issues as required.

Relevance of CJEU decision in C-630/10 Queensland

57 In C-630/10 *Queensland,* the CJEU clearly stated that if a basic patent relates to a process by which a product is obtained, Article 3(a) only allows an SPC to be granted for a product which is identified in the wording of the claims of the patent as the product deriving from the process in question. As explained above, the CJEU also stated that the grant of an SPC is not conditional on whether it is possible to obtain a product directly as a result of the process by which the product is obtained. The CJEU went on to state that whether it is possible to obtain the product directly as a result of the process is irrelevant[11].

58 The examiner has interpreted the CJEU's decision as meaning that the product of the SPC application must be identified in the wording of the claims of the basic patent as the product deriving from the process in question, and that the product for which the SPC is sought must or may be produced by the process as claimed in the basic patent.

[11] See paragraphs 40 and 41, and the Court's answer to the question referred in C-630/10, *University of Queensland, CSL Ltd v Comptroller-General of Patents, Designs and Trade Marks,*.

59 In contrast, the applicant interprets the CJEU's decision in C-630/10 as *only* requiring that the product for which the SPC is applied for must be identified in the wording of the claims of the patent as the product deriving from the process in question. They argue that there is no requirement for any subsequent step which requires confirmation that the product of the SPC application is produced by the method of the basic patent.

60 In looking at this question, I think that it is necessary to keep the following points in mind.

(a) Firstly, the claims in a patent are a matter for the applicant and the authority responsible for granting the patent, in this case the EPO. The final granted set of claims represent an invention that meets the requirements for patentability – in general terms, it is novel, inventive, is not excluded and is capable of industrial application. Thus, the product, process and/or use that is the subject of the patent may be identified using any language that the applicant and the examiner can agree on that meets the relevant legal requirements.

(b) Secondly, a marketing authorisation is confirmation that a medicinal product comprising an active ingredient meets the criteria for safety, efficacy and quality and has a positive risk-to-benefit profile for patients. While the MA may include some information on the production of the medicinal product, it does not normally include precise details about the individual components.

(c) Thirdly, it is increasingly common that the holder of the MA is not always the same entity as the holder of the patent.

(d) Fourthly, as a consequence of the latter point, both of these parties will have to enter into some sort of commercial arrangement which on the one hand allows the MA holder to use the patented product and, on the other allows the patentee, to recoup its investment in the work that led to the grant of the patent.

61 The applicant considers that the approach taken by the examiner which seeks to establish not just that the product for which the SPC application is sought is identified in the wording of the claims of the basic patent as the product deriving from the process claimed, but also that the process claimed in the basic patent is one that is or can be used to obtain the product for which the SPC is sought, is to take matters a step too far.

62 In the applicant's view, this latter point, i.e., could the process claimed in the basic patent be the one that is used to obtain the product for which the SPC is sought, relates more to what the SPC, once granted, protects under Article 5, and is not part of the consideration when deciding whether an SPC can be granted under Article 3 in the first place.

63 I would thus summarise the consequence of the applicant's view in the following terms: It is first necessary to confirm if the product which is the subject of the SPC application is identified both in the wording of the claims of the basic patent [see Article 3(a)] and as an active ingredient in the medicinal product which is the subject of the marketing authorisation (MA) [see Article 3(b)]. While, one also has to check that the product has not already been the subject of a certificate [see Article 3(c)]

and confirm that the MA provided in support of the application is the first authorisation to place this product on the market in the community [see Article 3(d)], it is articles 3(a) and 3(b) which are key to actually identifying whether the product for which the SPC has been applied for constitutes a valid application and may be granted. In the case at issue what we are concerned with is whether or not *Agalsidase-beta* which is the product for which the SPC is sought is identified in the wording of the claims of the basic patent EP(UK) 2210947 B1.

64 In its decision in C-630/10 *Queensland*, the CJEU referred to the fact that the product must be identified in the wording of the claims of the patent as '*the product deriving from that process*'[12]. By including a reference to the fact that the product must be identified as the product *"deriving from the process"*, it could be argued that the CJEU sought to provide the additional limitation that the product which is the subject of the SPC application must actually be derived by the process in the patent in order to satisfy the requirements of Article 3(a) of the Regulation.

65 Indeed, for a process claim, it could be considered to be perfectly logical to require that the product for which the SPC has been applied for should be capable of being produced by the claimed process, because the protection conferred by a process claim extends only to a product produced by that process. Such an interpretation of the CJEU's decision in C-630/10 would therefore be consistent with the protection conferred by a process claim in national patent legislation[13]. However, it must also be borne in mind that the SPC Regulation falls at the junction of patent legislation and legislation relating to the regulatory approval of medicinal products. Thus, consistency with relevant patent legislation is not the only consideration when interpreting the SPC Regulation. The regulatory system concerns medicinal products and their approval for use in patients and the product cannot be put on the market for human use until it has been determined that it has an appropriate risk-to-benefit profile i.e. that is does have a beneficial therapeutic effect. The common denominator between the two systems is the product.

66 Furthermore, it is important to note that the CJEU clearly stated in its decision in C-630/10 *Queensland* that the grant of an SPC is not conditional on whether it is possible to obtain a product directly as a result of the process which is the subject of the patent. To emphasise its point, it even went as far as stating that whether it is possible to obtain the product directly as a result of that process is irrelevant - see paragraphs 40 and 41 of this decision (see above). Thus, I do not see how I can interpret the CJEU's decision in C-630/10 Queensland as requiring anything other than that the product must be identified in the wording of the claims of the patent as the product deriving from the process in the patent. By explicitly stating that it is irrelevant whether or not it is possible to obtain the product for which the SPC is being sought directly as a result of the process, the CJEU has effectively excluded any alternative interpretation which could require evidence of whether the product has been or can be produced by the claimed process. The focus of the CJEU decision is thus on identifying what is the product for which the SPC is sought and is it identified clearly enough in the claims of the basic patent. It is not relevant for the purpose of establishing if the product is identified in a claim in the basic patent

[12] See paragraph 40, C-630/10 *Queensland*
[13] For example in UK this would be under Section 60 of Patents Act 1977

whether the claim refers to the product itself, or to a process for making this product or to a use of this product .

67 Consequently, after considering the CJEU's decisions in C-630/10 *Queensland* and C-322/10 *Medeva*, and the aims and objectives of the SPC Regulation, I am persuaded that the applicant's interpretation of C-630/10 *Queensland* is correct. The CJEU's decision in C-630/10 *Queensland* merely requires that the product of the SPC application is identified in the wording of the claims of the basic patent as the product deriving from the process in question. I do not believe that the CJEU's decision includes an additional requirement which involves confirmation that the product of the SPC application which is identified in the patent and in the marketing authorisation has to be produced by the method of the basic patent.

68 I find support for this interpretation from the Explanatory Memorandum[14] on the creation of a supplementary protection certificate for medicinal products, to which I was referred during the hearing. Page 10 of this document refers to the fact that the SPC Regulation should be '*a simple, transparent, system which can easily be applied by the parties concerned*'. Page 24 of this Memorandum (paragraph 48) states (emphasis added) that:

> 'Few documents are required. Apart from the request itself, a copy of the first authorization to place the product on the market in the State concerned is required as this enables the product to be identified. If this authorization is not also the first authorization to place the product on the Community market, a copy of the latter also has to be attached since the duration of the certificate will be calculated, in all Member States in which a certificate is applied for, by reference to this criterion alone.
>
> Information enabling the basic patent to be identified must also be provided.
>
> **The authority empowered to grant the certificate will have to verify that the authorization(s) and the patent refer to one and the same product.**
>
> Lastly, the application must contain a summary of the pharmacological properties of the product.'

69 The Explanatory Memorandum therefore indicates that the system should be simple, and that few documents should be required for an SPC application. I believe that my interpretation of the CJEU's decision in C-630/10 *Queensland* is consistent with these aims of the Explanatory Memorandum.

70 I find further support for my interpretation of C-630/10 *Queensland* from the decision by Arnold J in *Novartis*[9]. In this decision, Arnold J applied the CJEU's decision in C-630/10 *Queensland*, and specifically referred to the fact that it is irrelevant whether or not it was possible to obtain the product directly by means of the process. Paragraph 57 of his decision reads:

> *"Thirdly, even if Medeva can be interpreted as leaving open the possibility that it is sufficient for the product to be within the scope of the claim where the claim is*

[14] Proposal for a Council Regulation (EEC) concerning the creation of a supplementary protection certificate for medicinal products (presented by the Commission); COM (90) 101 final – SYN 255, Brussels, 11 April 1990.

a product claim, it seems to me that Queensland lays down a narrower rule in the case of process claims. The Court of Justice requires the product to be identified in the wording of the claim as the product deriving from the process in question. Furthermore, it says that it is irrelevant whether or not it was possible to obtain the product directly by means of that process, which points away from an infringement-type test. ***In the present case, claim 1 merely identifies the product of the method as "a molecule with binding specificity for a particular target". This covers millions of different molecules of various kinds. It is not even limited to antibodies. Although ranibizumab falls within this extremely broad class of products, there is nothing at all in the wording of the claim, or even the lengthy specification of the Patent, to identify ranibizumab as the product of the process in question."***

Whilst this aspect of the CJEU's decision in C-630/10 *Queensland* was not apparently a defining point in Arnold J's decision due to the facts of that case, the point was still considered to be important enough for Arnold J to refer to it in his decision.

71 In my opinion, this interpretation of C-630/10 *Queensland* also provides the additional advantage of ensuring that the assessment of Article 3(a) is consistent, whether the basic patent filed in support of the SPC application includes a process claim, a use claim or a product claim. The question to be answered in each case is whether the product is identified in the wording of the claims of the patent.

The product identified in the claims of the basic patent

72 The question which I must therefore now answer is whether, or not, the product for which the SPC is sought is identified in the wording of the claims of the patent as the product deriving from the process in question.

73 Counsel for the applicant presented the applicant's position as being that the claim of the basic patent filed in support of this SPC application relates to a recombinant, secreted, human α-Galactosidase A containing mannose-6-phosphate. They also argued that the reference to CHO cells in part (a) of the claimed process dictates that the recombinant, secreted, human α-Galactosidase A containing mannose-6-phosphate would also have the glycosylation profile associated with CHO cells.

74 Counsel then went on to explain how they considered *agalsidase-beta* (the product identified in the marketing authorisation filed in support of this SPC application) to be the same as or in their words 'commensurate with' the product specified in the claim of the basic patent. I was referred to the fact that the 'Summary of Product Characteristics' for *Fabrazyme*[15] states that *Fabrazyme* contains recombinant human agalsidase beta, which is a '*recombinant form of human α-Galactosidase A produced in CHO cells'*. I was then referred to the 'product monograph' for *Fabrazyme* that has been generated by Genzyme Corporation, a copy of which was filed as part of the initial application for this SPC. In particular, page 13 of this document states that *Fabrazyme* contains *'...consistent levels of both sialic acid and mannose-6-phosphate, two carbohydrates that affect the biodistribution of the*

[15] See entry for Fabrazyme on EMA website and, in particular, the EPAR – Product Information at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000370/WC500020547.pdf

enzyme and allow for appropriate lysosomal uptake...'[16]. Page 13 of this document also confirms that the enzyme *agalsidase-beta* is produced in CHO cells and secreted during the manufacture of *Fabrazyme*.

75 Consequently, the applicant argues that *agalsidase-beta* is commensurate with the product 'recombinant, secreted, human α-Galactosidase A containing mannose-6-phosphate produced in CHO cells' which is specified in the claim of the basic patent, because *agalsidase-beta* has been shown to be recombinant, secreted, human α-Galactosidase A, containing mannose-6-phosphate, expressed in CHO cells.

76 In considering the above argument, I would point out that I am not convinced that the 'secreted' aspect of the product definition in claim 1 is relevant to determining whether the product is identified/specified in the wording of this claim. As briefly discussed at the hearing, I believe that the product identified/specified in the wording of the claim is more accurately identified as recombinant human α-Galactosidase A containing mannose-6-phosphate and having the glycosylation profile which stems from its production in CHO cells.

77 It is clear from the above discussion that the claim of the basic patent does not actually use the words 'agalsidase beta', which is the product for which the SPC is sought. I must therefore decide whether the product in the preceding paragraph which I have stated is identified/specified in the wording of the claims of the basic patent is *agalsidase-beta*, as argued by the applicant.

78 The CJEU's recent decision in C-493/12 (*Eli Lilly)*[8] stated that a functional definition may suffice for a product to be protected by a basic patent (for the purposes of Article 3(a)) if "*the claims relate, implicitly but necessarily and specifically to the active ingredient in question*". As such, I believe that the CJEU's decision in C-493/12 provides a clear indication that it is not necessary for the claim of the basic patent to use identical wording to the marketing authorisation when specifying/identifying the product for which an SPC is sought. Consequently, whilst the claim needs to specify/identify the product for which an SPC is sought[17,18,19], it is apparent that the claim does not need to expressly refer to the product by the same name as is referred to in the application for the SPC, in this case, *agalsidase-beta*. For the purposes of Article 3(a), it is sufficient for the claim to specify/identify *agalsidase-beta* in some other suitable way.

79 As already noted above, in the *Novartis*[9] decision, Arnold J applied C-630/10 *Queensland* and concluded that the product for which an SPC was being sought, the antibody *ranibizumab,* was not identified in the wording of the claim of the patent as the product deriving from the process in question. In reaching his decision that the SPC in question was invalid, Arnold J noted that claim 1 merely *"...identifies the product of the method as 'a molecule with binding specificity for a particular target'..."* and went on to state that *"...Although ranibizumab falls within this extremely broad class of products, there is nothing at all in the wording of the claim, or even the lengthy specification of the Patent, to identify ranibizumab as the product of the*

[16] http://www.fabrazyme.com/hcp/support/Fabrazyme_Product_Monograph.pdf
[17] C-322/10 *(Medeva)*
[18] C-630/10 (*University of Queensland)*
[19] C-493/12 (*Eli Lilly.)*

process in question...". The claim of the basic patent filed in support of the present SPC application clearly provides a more specific definition of a product than the claims considered by Arnold J in *Novartis.* Consequently, I believe that the present case is distinguished from the situation considered in *Novartis*.

80 I am satisfied that *agalsidase-beta* is the product which is identified in the wording of the single claim of the basic patent EP(UK) 2210947 B1. *Agalsidase-beta* clearly shares all of the features of the product which is identified in the wording of the claims of the basic patent. The description of the product identified/specified in the claim of the patent is also suitable for distinguishing this product from other closely related forms of α-Galactosidase A, such as *agalsidase-alpha*. The latter form of α-Galactosidase A is not produced in CHO cells and does not therefore have the same glycosylation profile as *agalsidase-beta* and the product identified in the claim of the basic patent.

81 I find additional support for my conclusion in the EPAR scientific discussion document[20] for *Fabrazyme* discussed by the relevant committee of the European Medicines Agency (EMA) as part of its assessment of the marketing authorisation application. In this document, I note that the following statements are used to describe *Fabrazyme* –

(a) *Fabrazyme* is a recombinant human α-galactosidase (r-hαGAL), INN: agalsidase beta, which is produced by genetically engineered Chinese Hamster Ovary (CHO) cells;

(b) Recombinant hαGAL is a highly purified recombinant form of the naturally occurring human lysosomal hydrolase enzyme responsible for the metabolism of globo-triaosyl-ceramide (ceramide trihexoside; CTH; GL-3)

(c) After administration, *agalsidase-beta* is rapidly removed from the circulation and taken up by vascular endothelial and parenchymal cells into lysosomes, likely through the mannose-6-phosphate, mannose and asialoglycoprotein receptors. The proposed indication of *Fabrazyme* is long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease

(d) *Fabrazyme* is a lyophilised sterile dosage form. The active substance *agalsidase-beta* is produced by recombinant DNA technology. *Agalsidase-beta* is produced by mammalian cell culture using a Chinese Hamster Ovary (CHO) cell line co transfected with a recombinant plasmid containing DNA sequences encoding the α-galactosidase protein.

Thus the active ingredient in the approved medicinal product, *Fabrazyme*, is being described using identical terms as are being used to identify the secreted protein in the method of claim 1 of the basic patent (see above)

82 In my opinion, the definition of the product in the claim of the basic patent is therefore a definition which is suitable for identifying *agalsidase-beta*. As such, the product for which the SPC is sought (*agalsidase-beta*) is suitably identified in the

[20] See entry for Fabrazyme on EMA website and in particular the EPAR – Scientific Discussion at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000370/WC500020543.pdf

wording of the claims of the patent as the product deriving from the process in question. Thus, I consider that this application meets the requirements of Article 3(a) of the Regulation.

83 Notwithstanding the above analysis, I note that there may be some occasions where it is necessary to confirm that a product can be obtained by a process claimed in the basic patent when considering Article 3(a) of the Regulation, for example if the product is not clearly specified/identified in the wording of the claims of the basic patent. As I have already noted, this is not such an instance and I am satisfied that the product is specified/identified in the wording of the claim of the basic patent.

The Applicants 'Fall-back' Positions

84 In light of my interpretation of the CJEU's decision in C-630/10 (*University of Queensland*) and my conclusion that the product is identified in the claims of the patent as the product deriving from the process in question, further discussion of the issue of whether the product *agalsidase-beta* could be, or indeed is, produced by the method claimed is not necessary.

85 However, for completeness, I will simply state that even if I had not agreed with the applicant's interpretation of C-630/10 *Queensland*, I do think it is likely that the present SPC application would still meet the requirements of Article 3(a) of the Regulation because I believe that the product *agalsidase-beta* could be produced by the method claimed in the basic patent. As discussed in the technical background section above, *agalsidase-beta* (a recombinant form of human α-Galactosidase A) is a complex mixture of different glycoforms within a consistent profile of glycosylation which is produced by CHO cells. On balance, I believe that the claimed method, which utilises CHO cells to produce recombinant human α-Galactosidase A, would produce a mixture of glycoforms which would be likely to be broadly consistent with the mixture of glycoforms present in *agalsidase- beta*.

86 I was addressed at some length in the hearing on the question of whether or not the claimed method requires the use of 1000 µM methotrexate (MTX) to culture the CHO cells, and whether the manufacturing process for the medicinal product which had been granted a marketing authorisation utilised such a MTX concentration (full manufacturing details of the authorised medicinal product were not available from the third party in their observations although they are the company that actually produces the medicinal product *Fabrazyme*). This was an issue which was discussed in detail during the examination of the SPC application, and which was relevant to the applicant's fall back positions if I did not agree with their interpretation of C-630/10 *Queensland* (see discussion above). In light of my conclusions on how C-630/10 *Queensland* should be interpreted, the discussions about the MTX concentrations required by the claim were not relevant to my assessment of whether the application meets the requirements of Article 3(a).

Other Matters

87 At my request, I was also addressed during the hearing on the differences between *agalsidase-beta* (α-Galactosidase A produced in CHO cells) and agalsidase alpha (α-Galactosidase A produced in human cells). Based on the technical background, which I have summarised above, I am content that these active ingredients are

different products for the purposes of the SPC Regulation because of the differing characteristic glycosylation profiles on the enzyme when it is produced in the different cell types. I am therefore of the opinion that each product can be the subject of a separate SPC, and that the requirements of Article 3(c) are satisfied.

Conclusion

88 Taking all of the above into account, I consider that the product for which an SPC is sought, *agalsidase-beta*, as referred to in Patents Form SP1 filed with application SPC/GB13/069, is identified in the wording of claim 1 of the basic patent EP(UK) 2210947 B1 as the product deriving from the process described.

89 Thus, I consider that the basic patent protects the product for which the SPC is sought and so this SPC application meets the requirement of Article 3(a) of the SPC Regulation.

90 I remit the application back to the examiner to make the necessary arrangements to grant the SPC.

Appeal

91 Any appeal must be lodged within 28 days.

Deputy Director, acting for the Comptroller