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11 December 2012

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

APPLICANT	Genzyme Corporation
ISSUE	Whether SPC application number SPC/GB/09/057 complies with Article 3 and may be granted
HEARING OFFICER	Dr P Purcell

DECISION

Introduction

1. This decision relates to an application for a supplementary protection certificate (SPC) which was filed by Genzyme Corporation ("the applicant") on 9 September 2009 and accorded the number SPC/GB/09/057. The product in respect of which the SPC is sought comprises a single active component, namely "Sevelamer Carbonate or Bicarbonate" as identified on form SP1 at item 6.

2. The basic patent upon which the application relies is EP (UK) 0 716 606 B1, which was filed on 10 August 1994 with an earliest priority date of 11 August 1993, and was granted on 29 August 2001. It is accepted that claim 1 of the basic patent covers Sevelamer Carbonate or Bicarbonate, albeit identified in the form of a chemical structure.

3. The European marketing authorisation (MA), EU/1/09/521/001-7, for the medicinal product "Renvela", supplied in support of the application, was granted on 10 June 2009 by European Commission Decision C(2009)4621. This MA is valid within the UK.

4. In their initial application form SP1 and accompanying letter, dated 9 December 2009, the applicant identified this European MA as the relevant MA for the purposes of making the present application.

5. The view of the examiner, Dr Jason Bellia, first expressed in his examination report dated 22 November 2010, was that the product which was the subject of the present application was already protected by an earlier certificate, SPC/GB/02/011,

granted to the same applicant and which identified the product protected by the certificate simply as sevelamer. Furthermore, the examiner objected that the authorisation supplied in support of this present application was not the first authorisation to place the product on the market in the community. Thus neither of the conditions set out in Articles 3(c) and 3(d) of 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 ("the Regulation") had been met by the application. Consequently, the examiner's view was that the applicant was not entitled to a further certificate arising from this application as a certificate had already been granted that protected the product and that any additional term of protection would extend beyond 15 years and thus offend Recital 9 of the Regulation.

6. The earlier SPC identified by the examiner also relied upon the same basic patent, EP (UK) 0 716 606 B1 as the current application, but cited as the first marketing authorization EU/1/99/123/001-004 for the medicinal product "Renagel" which was granted on 28 January 2000 by European Commission Decision C(2000)119. The active ingredient in this medicinal product is identified as sevelamer, albeit in a hydrochloride form. In the opinion of the examiner the presence of this different form of sevelamer, with the hydrochloride counter ion rather than the carbonate form for which protection is being sought in SPC/GB/09/057, does not distinguish the active ingredients.

7. In support of his view that the earlier SPC encompasses sevelamer carbonate, the examiner cited the judgement of the Court of Justice of the European Union (CJEU) in case C-392, *Framitalia Carlo Erba Srl*. In further correspondence with the applicant, he also made reference to the decision of Jacob J (as he was then) in the Patents Court in *Draco AB's SPC Application* [1996] RPC47 and also the Advocate-General's (AGs) Opinion in CJEU case C-130/11, *Neurim Pharmaceuticals (1991) Ltd v Comptroller General of Patents*.

8. The examiner and the applicant both agree that the basic patent EP (UK) 0 716 606 protects both anion salts of the active ingredients present in the medicinal products "Renvela" and "Renagel", as set out in the agent's letter of 12 April 2011. However, in response to the examiner's objections the applicant arguments were, as summarized in their agent's letter of 12 December 2011that:

"...whilst Renagel (sevelamer hydrochloride) and Renvela (sevelamer carbonate) are both anion exchange resins with "sevelamer" as the polymer backbone, they contain different anions and, accordingly, are different active ingredients."

9. The applicants further supported this argument in their agent's letter by pointing out that the EMA whilst approving the two different medicinal products for use in controlling the same condition, hyperphosphataemia, distinguished the use of these medicinal products between different patient groups, "Renagel" being only approved for use in adults undergoing dialysis whereas "Renvela" is approved for use not only in patients on dialysis but also those with chronic kidney disease who are not on dialysis. The applicants argued in their agents' letter of 12 December 2011 that the replacement of the chloride ion with carbonate "mitigates the acid-base disturbance and provides a compound more suitable for treating

hyperphosphataemia CKD patients not on dialysis and paediatric patients". Further the applicant stated that they had consistently taken this approach concerning the different nature of "Renagel" and "Renvela". In support of these arguments the applicants supplied a number of scientific journal articles, the European Public Assessment Report (EPAR) for both "Renvela" and "Renagel" and a document prepared by the applicant entitled "Sevelamer carbonate Common Technical Document Section" (the CTD).

10. The examiner did not accept these arguments and reiterated his objections in his examination report of 11 June 2012, and so the applicant in their letter dated 12 October 2012, requested that a decision be made based upon the papers on file.

11. The issues to be decided are thus; whether the conditions of Articles 3(c) and (d) of the Regulation have been met and the application can proceed to grant.

The law and its interpretation

12. 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 ("the Regulation"), see OJ L 152, 16.6.2009, p 1, codified and superceded Regulation (EEC) No. 1768/92 concerning the creation of a Supplementary Protection Certificate for Medicinal Products .

13. Recitals 1-6, 9 and 10 of the Regulation state:

> *(1) Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products [OJ 1992 L 182, p. 1] has been substantially amended several times. In the interests of clarity and rationality the said Regulation should be codified.*
> *(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 4 ["MA"] makes the period of effective protection under the patent insufficient to cover the investment put into the research.*
> *(5) This situation leads to a lack of protection which penalises pharmaceutical research.*
> *(6) There exists a risk of research centres situated in the Member States relocating to countries that offer greater protection.*
> *…*
> *(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 [MA] 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 strictly confined to the product which obtained authorization to be placed on the market as a medicinal product*

14. Article 3, parts (b), (c) and (d) of the Regulation provide 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:

(b) a valid authorization 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"

wherein "medicinal product" and "product" are defined in Article 1 of the Regulation as follows:

For the purposes of this Regulation:

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

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

15. Thus, the effect of Article 3(c) is that a request for a certificate for a product, that is an active ingredient or combination of active ingredients of a medicinal product, cannot be granted if that product is already the subject of a certificate when the request is made.

16. Article 10 provides that:

"(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) ….. "

17. Also relevant are recitals 13, 14 and 17 of Regulation (EC) No 1610/96 of the European Parliament and of the Council (plant protection products) ("the Plant Protection Regulation"):

(13) Whereas the certificate confers the same rights as those conferred by the basic patent; whereas, consequently, where the basic patent covers an active substance and its various derivatives (salts and esters), the certificate confers the same protection;
(14) Whereas the issue of a certificate for a product consisting of an active substance does not prejudice the issue of other certificates for derivatives (salts and esters) of the substance, provided that the derivatives are the subject of patents specifically covering them;
(17) Whereas the detailed rules in recitals 12, 13 and 14 and in Articles 3(2), 4, 8(1)(c) and 17 (2) of this Regulation are also valid, mutatis mutandis, for the interpretation in particular of recital 9 and Articles 3, 4, 8(1)(c) and 17 of Council Regulation (EEC) No 1768/92,

18. In determining the scope of a certificate the decision of the European Court of Justice in *Farmitalia Carlo Erba Srl's SPC Application* (C-392/97) [2000] RPC 580 (hereafter *"Farmitalia"*) is particularly relevant, where the Court found that:

> On a proper construction of Council Regulation EEC No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products and, in particular, Article 3(b) thereof, where a product in the form referred to in the marketing authorisation is protected by a basic patent in force, the supplementary protection certificate is capable of covering the product, as a medicinal product, in any of the forms enjoying the protection of the basic patent.

19. In the judgement on *Farmitalia* the Court made the following comments making clear that a certificate can protect all forms of an active ingredient that fall within the scope of the basic patent and thus is not necessarily restricted to the specific salt or ester that has been approved in the marketing authorization relied upon:

17. By its first question, the national court asks, in substance, whether, on a proper construction of Article 3(b) of Regulation No 1768/92, the certificate can protect the product only in the specific form stated in the marketing authorisation.

18. In that regard, all the interested parties who have submitted observations have maintained, in particular, that while the certificate could protect only the particular salt form of the active ingredient mentioned as the active constituent in the marketing authorisation, whereas the basic patent protects the active ingredient as such as well as salts thereof, including the one which is the subject-matter of the marketing authorisation, any competitor would be able, after the basic patent had expired, to apply for and, in some circumstances, obtain marketing authorisation for a different salt of the same active ingredient, formerly protected by that patent. It would therefore be possible for medicinal products which were, in principle, therapeutically equivalent to that protected by the certificate to compete with the latter. The result would be to frustrate the purpose of Regulation No 1768/92, which is to ensure the holder of the basic patent of exclusivity on the market during a given period extending beyond the period of validity of the basic patent.

19. That line of argument must be accepted. If the certificate did not cover the actual medicinal product, as protected by the basic patent and one of the possible forms of which is the subject-matter of a marketing authorisation, the fundamental objective of Regulation No 1768/92, as set out in the first and second recitals in the preamble thereto, which is to provide for sufficient protection to encourage research in the pharmaceutical field, which plays a decisive role in the continuing improvement in public health, could not, for the reasons set out in paragraph 18 of this judgment, be attained.

20. Moreover, it should be borne in mind that the 13th recital in the preamble to Regulation (EC) 1610/96 of the European Parliament and of the Council of 23 July 1996 which, by virtue of the 17th recital, is also valid, *mutatis mutandis*, for the interpretation *inter alia* of Article 3 of Regulation No 1768/92, states that the certificate confers the same rights as those conferred by the basic patent, with the result that, where the basic patent covers an active substance and its various derivatives (salts and esters), the certificate confers the same protection.

21. Accordingly, where an active ingredient in the form of a salt is referred to in the marketing authorisation concerned and is protected by a basic patent in force, the certificate is capable of covering the active ingredient as such and also its various derived forms such as salts and esters, as medicinal products, in so far as they are covered by the protection of the basic patent.

20. Furthermore in determining the purpose behind the Regulations I am also aided by the relevant *travaux préparatoires*. These include the Commission's proposal for a Medicinal Products Regulation (COM (90) 101 Final) and its later proposal for a Plant Protection Products Regulation (COM (94) 579 Final) were each supplemented by an Explanatory Memorandum. Although the texts of these Regulations were modified before they were finally adopted, this does not mean that the Explanatory Memoranda ceased to be relevant to interpreting the Regulations.

21. In paragraph 36 of the Explanatory Memorandum concerning the proposal for a Medicinal Products Regulation the Commission explained the purpose underlying Article 3(c) (my emphasis added):

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

22. This statement thus appears to confirm the interpretation of the Regulation set out in *Farmitalia* that an SPC can protect the active ingredient in all its derived forms as well as that in the medicinal product approved and relied upon for the grant of the SPC. It also makes clear that although the product may be the subject of several marketing authorizations only the earliest one should be relevant for determining the duration of the certificate.

23. The most relevant case in the United Kingdom is *Draco AB's SPC Application* [1996] RPC47 (hereafter "*Draco*"). In this decision of Jacob J (as he was then) in the Patents Court found that the presentation of an known product, Budesonide, in the form of additive free agglomerated particles rather than the earlier formulation as an aerosol was not capable of being protected by an SPC as this was merely a reformulation. He rejected an argument that this reformulation was a different product because of the different efficacies of the two presentations (see page 439, lines 39-42) and went on to state at page 439, lines 48-52:

> I see nothing to indicating that formulation research (unless of course it warrants its own patent) is to be protected by the SPC scheme. The scheme is not for the general protection of the fruits of research. It is to compensate for lost time in the exploitation of inventions which are patented.

24. Jacob J further made the point that the SPC system should not be one where an SPC for a product could be evaded because of a new formulation of an active ingredient. The SPC should provide protection against this different formulation even if it required a new authorization to be placed on the market otherwise "it would blow a vast hole in the SPC system." (page 439, line 31). This observation is consistent both with the comments of the CJEU expressed in *Farmitalia* at paragraph 18 that if pharmaceutically equivalent products could be marketed even if a certificate was in force then the purpose of the Regulation would be frustrated, as well as the purpose as set out in paragraph 36 of the Explanatory Memorandum set out above.

Discussion and argument

The objections concerning Article 3(c)

25. As I have noted above it is common ground that the basic patent EP (UK) 0 716 606 protects sevelamer as both the sevelamer hydrochloride and sevelamer carbonate salts. The invention of this basic patent is concerned with, as summarized in the "Summary of the invention", paragraph 0007 removing phosphate from a patient by administration of phosphate binding polymers such as sevelamer. As paragraph 0014 of this patent discloses the carbonate and chloride counter ions are amongst many different alternatives that may be present with the polymer, although no particular advantages of any counter ion are suggested. Consequently following the judgement of the CJEU in *Farmitalia* as set out above granted SPC/GB/02/011 is capable of protecting sevelamer in those forms that are protected by the basic patent. As the examiner has objected, this would encompass both the different anion forms of sevelamer that have been approved in the medicinal products "Renvela" and "Renagel". If this granted SPC does indeed protect both forms of sevelamer and they are not to be considered as separate products, then the condition for grant of the current application set out in Article 3(c) will not have been met, because the product has already been the subject of a certificate and a further certificate cannot be granted.

26. Therefore in order to determine whether the already granted certificate SPC/GB/02/011 encompasses sevelamer carbonate, or this is indeed a different product as claimed by the applicant and not simply a reformulation with a further anion, I need to consider the evidence presented in the papers on this issue.

27. As set out by the examiner in his letter of 11 June 2012 "The Summary of Product Characteristics" (SmPC) for the medicinal product "Renvela" makes clear at several sections, for example "Section 5.1, Pharmacodynamic Properties", that this medicinal product contains the same active moiety as sevelamer hydrochloride. The actual active ingredient that has the required phosphate binding effect is the sevelamer polymer which contains multiple amines that, when protonated in the stomach of a patient, can bind free phosphate thereby lowering the serum phosphate concentration. The counter ion, whatever its nature, does not itself contribute to this role. The subsequent "Section 5.2 Pharmokinetic Properties" of the SmPC states that these studies have not been carried out with sevelamer carbonate. Instead both this section and "Section 5.3 Preclinical Safety Data" rely at least in part on data

obtained from sevelamer hydrochloride as evidence that these requirements have been met. This approach is confirmed by the disclosures in the applicant's own document the CTD at section 2.5.1.1 which states on page 9 that "The demonstration of equivalence between the two salts allows the use of the sevelamer hydrochloride data to support the MAA for Renvela (sevelamer carbonate)."

28. Further the CTD makes clear at page 8 for example, that "While the anions differ for the two salts, the polymer which is the active moiety responsible for binding of phosphate, is the same.". This statement is also repeated at page 49 of the CTD in section 2.5.6.1.1. This section then makes clear that the advantage of this new presentation is "The removal of the chloride ion and its replacement with carbonate" which "mitigates the acid-base disturbance and provides a compound more suitable for treating hyperphosphate CKD patients not on dialysis and paediatric patients."

29. Moreover at page 21 this document states that "Sevelamer hydrochloride and sevelamer carbonate are similarly protonated after exposure to stomach contents, and thus will be presented as identical polymers to the intestinal lumen of the lower gastrointestinal tract where drug interactions can occur." This statement is also repeated at page 52 of the CTD. Similarly at page 49 in section 2.5.6.1.1. the product is described thus "While the anions differ for the two salts, the polymer which is the active moiety responsible for biding of phosphate, is the same." and the document concludes on page 53 with the statement that "... sevelamer carbonate is a new sevelamer salt with a more favourable benefit risk profile compared with sevelamer hydrochloride..."

30. In addition the CTD in Section 2.5.4.2.1. makes clear that sevelamer carbonate and sevelamer hydrochloride when taken in an identical dosage regime of three times per day are equivalent in terms of the control serum phosphorus and thus treating hyperphosphataemic haemodialysis in patients, which is the indication both medicinal products have been approved for. As Section 2.5.6.1 of the CTD makes clear that the benefits of the carbonate salt over the hydrochloride lie in this alternative salt mitigating the risk of worsening metabolic acidosis when the medicinal product is used and not in treating any new condition. This enables Renvela to be used by a broader patient group regardless of their dialysis status. In the agent's letter of 12 December 2012 it is argued that this "enhanced safety profile" results in the EMA differentiating between the medicinal products "Renagel" and "Renvela" and so the applicant consider these to relate to different active ingredients.

31. It is clear from the information presented above that whilst the EMA has approved two separate medicinal products in "Renvela" and "Renagel", both are used to treat the same indication hyperphosphataemic haemodialysis albeit in different patient groups although these groups overlap. However, the fact that one medicinal product has an "enhanced safety profile" over the other does not indicate that the active ingredient in these medicinal products is different. I believe that the evidence supplied by the applicant does not show that the active ingredient is a new product, rather it consistently makes clear that the active ingredient presented to treat the indication hyperphosphataemic haemodialysis is the same polymer in both "Renvela" and "Renagel". This polymer is the sevelamer component which performs

the same function in the same way regardless of which medicinal product is used and moreover the same form of the polymer is made available in the body to perform the required phosphate binding role. The differences in the two medicinal products lies in the presence of the respective anions which do not in themselves act to treat the indication. Rather this change in anion as the applicant's CTD document explains mitigate and thus overcomes the potential for metabolic acidiosis which is described as a safety concern (see page 49 of the CTD).

32. This development of sevelamer appears to be the type of work identified by Jacob J in *Draco* as formulation research that falls outside the scope of the SPC Regulation- no new active ingredient has been brought to the market and no new condition is being treated, that is to say there is no new application of the product, and the new formulation is not the subject of its own patent- in fact both forms are protected by the same basic patent. Thus I believe sevelamer carbonate cannot be considered to be a distinct active ingredient in its own right. Rather the active ingredient as defined in Article 1(b) for the purposes of the Regulation is the sevelamer component, irrespective of which anion it is complexed with and this component is the same whether present in the medicinal products "Renagel" or "Renvela". The later formulation brought to the market seeks to overcome other issues but does not alter the role, activity or effectiveness of sevelamer.

33. Consequently, I conclude that following the decision of the CJEU in *Farmitalia* and considering Recital 13 of the Plant Protection Regulation which applies by virtue of Recital 17 of said Regulation, the granted certificate SPC/GB/02/011 protects the active ingredient sevelamer when complexed with different salts which includes the carbonate salt as well as the originally approved hydrochloride salt. Therefore the present application does not meet the condition for grant set out in Article 3(c) of the Regulation that the product has not been the subject of an earlier certificate and so should be rejected as required by Article 10(2).

The objections concerning Article 3(d)

34. For completeness I will now consider the objection that the examiner also raised concerning compliance with Article 3(d) of the Regulation. The examiner in his reports found that because he considered the product to be sevelamer the condition set out in Article 3(d) was not met because the marketing authorization for "Renvela" is not the first authorization for the active ingredient sevelamer. For the reasons set out above I have agreed with the opinion of the examiner about the nature of the active ingredient and that the presence of a different counter ion in the medicinal product "Renvela" does not distinguish the active ingredient from the previous authorized form. Therefore because I consider the product is the sevelamer polymer I also consider that the condition set out in Article 3(d), that the authorisation is the first authorisation to place the product on the market as a medicinal product, is not met because the active ingredient was first authorised in the medicinal product "Renagel" even though it was formulated with the hydrochloride counter ion.

35. However, if I have interpreted the law incorrectly and sevelamer carbonate is indeed a different product that can be distinguished from sevelamer on the basis of

the different anion salt it would not fall within the scope of the earlier granted SPC and so the condition set out in Article 3(c) would be met. As I have noted previously this product is protected by the basic patent as required by Article 3(a) of the Regulation. Therefore it would also follow that the marketing authorization for the medicinal product “Renvela” allowing this active ingredient sevelamer carbonate to be placed on the market would also be the first marketing authorization for the purposes of Article 3(d) of the Regulation. The marketing authorization for the medicinal product “Renagel” would not be relevant under Article 3(d) for the purposes of this application. Therefore any certificate that could be granted would be for the specific active ingredient sevelamer carbonate and would have to rely upon the authorization for the product “Renvela” in order to determine the maximum expiry date of the certificate under Article 13(1) of the Regulation, although for the reasons set out above I do not believe this is the case.

Conclusion

36. I conclude that the present application does not meet the conditions set out in the Regulation in Article 3(c) that the product has not been the subject of an earlier certificate and also Article 3(d) that the authorisation is the first authorisation to place the product on the market as a medicinal product. As a result of the objection under Article 3(c) the present application should be rejected as required by Article 10(2) of the Regulation.

Appeal

37. Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days.

Dr P PURCELL
Deputy Director acting for the Comptroller