Decision in Respect of a Request by Novo Nordisk A/S for the Grant of a Supplementary Protection Certificate (SPC) No. 2013/035

INTRODUCTION

1. This decision concerns a request for the grant of SPC No. 2013/035 filed on 15 July 2013 on behalf of Novo Nordisk A/S (applicant) by Tomkins & Co. (agent) for the product RYZODEG, a *"Combination of insulin degludec and insulin aspart in all its forms as they are protected by the basic patent."* The basic patent cited in support of the request was European Patent EP2107069 with the title *"Novel insulin derivatives."* In relation to this patent, the applicant stated that: "*Patent No. 2107069 protects the product by at least claim 1 and specifically by at least claim 11 of the basic patent".*

2. In support of the request, the agent submitted - a copy of the Commission Implementing Decision of 21 January 2013 granting five marketing authorisations (MAs) to Novo Nordisk A/S for *"Ryzodeg - insulin degludec and insulin aspart", namely EU/1/12/806/001, 004, 005, 007 and 008*. In addition, the agent requested that the examination be deferred pending a judgment in the case C-443/12 *Actavis Group PTC EHF & Actavis UK Ltd. v Sanofi* (*Sanofi*).

3. The legislation governing SPCs is Council Regulation (EEC) No. 1768/92 concerning *"the supplementary protection certificate for medicinal products."* This was amended by the Paediatric Regulation to provide for a further 6-month extension and was codified as Regulation (EC) 469/2009 – hereinafter the *'SPC Regulation'*.

4. On 25 February 2014 the agent wrote to the examiner to request that examination of this application be further stayed pending a decision from the Court of Justice of the European Union (CJEU) in the case C-577/13 *Actavis Group PTC EHF and Actavis UK Ltd v. Boehringer Ingelheim Pharma GmbH & Co. KG* (*Boehringer*). This request was duly granted.

5. The examiner wrote to the agent on 10 June 2016 to report that the CJEU had

issued its judgment in *Boehringer* on 12 March 2015 and quoted the ruling from paragraph 42: - *"Article 3(a) and (c) of Regulation (EC) No 469/2009 of the European Parliament and of the Council of 16 May 2009 concerning the supplementary protection certificate for medicinal products 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 a supplementary protection certificate, 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 supplementary protection certificate for that combination."*

6. The examiner noted that, in the present case, protection was being sought for a combination of two active ingredients, namely, insulin degludec and insulin aspart. Further, she stated that an SPC (No. 2013/034) had already been granted to the applicant for insulin degludec. Moreover, she noted that the second active component of this combination, i.e. insulin aspart, had previously been identified as an active ingredient in several other medicinal products, some of which had already been on the market for more than 10 years. She concluded that, as the CJEU had ruled a second SPC could not be granted for a combination product in such a case, she proposed to reject the application.

7. On 23 September 2016, the agent responded and cited the CJEU judgment in case C-617/12 *Georgetown University v Octrooicentrum Nederland (Georgetown)*. He pointed out that in this case the CJEU had ruled that it was possible to obtain two SPCs from the same basic patent, but that the court had not provided a general test.

8. The agent explained that, unlike in both *Actavis* and *Boehringer* judgments, the co-formulation comprising insulin degludec and insulin aspart was claimed explicitly in claim 11 of the basic patent. He emphasised how this co-formulation product, Ryzodeg, represented a totally separate invention compared to the insulin degludec on its own and, citing a publication "*Insulin degludec/insulin aspart combination for the treatment of type 1 and type 2 diabetes" by Angel Dardano et al., Vascular Health and Risk Management, 2014:10 465-475 (Dardano),* he summarised how and why the two insulins could be combined into a single product.

9. The agent confirmed that Ryzodeg was the first such product to successfully combine two different insulin analogues into a single formulation with the benefit to the diabetes patient being a reduction in the number of daily injections. He concluded that, as this combination of insulin degludec and insulin aspart was clearly another *"subject matter of the patent"* and represented a further *"core inventive advance"*, a second SPC should be granted. Finally, he reported that, to date, the same SPC request had been granted in 14 European countries and was pending in at least 11 others.

10. On 5 September 2018 the examiner responded by rejecting the arguments made by the agent and restated her intention to reject the SPC request. The agent replied on 7 September 2018 requesting a hearing on the case and this was arranged for 23 November 2018.

11. Prior to the hearing, the agent filed a further submission on 22 October 2018 providing additional technical information, case law and argumentation in support of the applicant's case.

12. In this submission the agent noted that, if granted, the present SPC would obtain the same expiry date as that granted for the mono-product, insulin degludec. Accordingly, he argued that there would be no unjustified exploitation of the SPC Regulation which he claimed the CJEU had been citing as a main reason for not granting combination SPCs and the interests of the public health (see the examiner's citation from *Boehringer* that an SPC should *be "balancing the interests of the pharmaceutical industry and the public health")* would not be impaired by its grant. He also updated the situation across Europe to the extent that the SPC had now been granted in 16 European countries with 10 applications still pending, and no application had been refused.

13. The agent reiterated that the present case distinguished itself from *Boehringer* because insulin degludec was not the "sole subject matter" of the basic patent. Furthermore, he regarded the requirements set out by the CJEU in judgment C-121/17 *Teva UK Ltd and others v Gilead Sciences Inc.* (*Teva*) as being satisfied, because claim 11 explicitly mentioned the combination product. He concluded that the present application fulfilled the criteria specified in the CJEU judgment. The agent did not accept

the examiner's conclusion that the combination did not comprise "active ingredients" constituting the subject-matter of the invention because this combination was clearly and explicitly covered by claim 11. He cited Article 84 of the European Patent Convention (EPC) on the scope of protection provided by the claims of a European patent, and the fact that the Irish Patents Act was entirely consistent with the EPC in this respect. He concluded that EPO had clearly found that insulin degludec, as well as the co-formulation with insulin aspart, were patentable subject matter within the requirements of the EPC and, likewise, with Irish law.

14. Commenting on the examiner's opinion that the co-formulation of insulin degludec and insulin aspart was not "inventive", the agent remarked that such a determination was outside the requirements of the SPC Regulation itself. He noted that in the referral that led to the CJEU judgment in *Teva*, the UK judge had suggested an additional requirement to the extent that the product in question *"embodies the inventive advance (or technical contribution) of the basic patent."* However, he observed that this suggestion had not been adopted in the judgment, but rather the CJEU had stated that the criteria were that the combination of those active ingredients must necessarily, in the light of the description and drawings of that patent, fall under the invention covered by that patent, and that each of those active ingredients must be specifically identifiable, in the light of all the information disclosed by that patent. The agent reaffirmed his position that the combination in claim 11 did indeed fulfil these criteria.

15. The agent observed that paragraph [0001] of the basic patent and cited by the examiner stated: *"The present invention relates to novel human insulin derivatives, … The invention also relates ..., to pharmaceutical compositions containing them…."* He claimed this meant that the invention related to both insulin degludec as well as to pharmaceutical compositions containing insulin degludec - Ryzodeg was a product being such a pharmaceutical composition containing insulin degludec. Furthermore, the agent reported that, to this day, Ryzodeg remained the first and the only combination product on the market containing two different insulin compounds within the same pharmaceutical composition.

16. Referring to the part of the European Medicines Agency CHMP Assessment Report for Ryzodeg as cited by the examiner, the agent explained that this same citation

spelt out clearly the remarkable feature of Ryzodeg – namely, that the two different insulins kept their individual activity without interactions in the combination formulation or subcutaneously upon injection.

17. The agent referred again to the *Dardano* reference from 2014 to explain in more detail how and why the other long-acting insulin analogues, namely detemir and glargine, could not be combined with insulin aspart. He pointed out that insulin glargine (IGlar) is most soluble in slightly acidic conditions (at a pH of 4) but rapid-acting insulins, such as insulin aspart (IAsp), are known to become unstable at a slightly acidic pH. He further stated that this was well known in the art and cited a statement from the American Diabetic Association in 2003 that "*Insulin glargine should not be mixed with other forms of insulin due to the low pH of its diluent.*" In relation to insulin detemir (IDet) he noted that, while it was soluble at the same pH as insulin aspart, it *"is formed from self-associated structures and when mixed with insulin aspart could form hybrid hexamers with unpredictable pharmacodynamics and pharmacokinetics"* as explained in the *Dardano* reference. Finally he further quoted from *Dardano* to highlight that *"…, currently existing basal insulin analogs (IGlar and IDet) are not available as combination formulations with fast-acting insulin analogs";* and, *"Another unique pharmacological property of IDeg (insulin degludec) is that is can be coformulated with insulin aspart (IAsp), resulting, for the first time, in a soluble preparation containing two different insulin analogs."*

18. The agent again referred the UK judge's suggestion of a test to the CJEU in *Teva* along the lines that the product in question *"embodies the inventive advance (or technical contribution) of the basic patent"* had not been adopted by the court. He said that that, even if this test were to be applied in the present case, the ability to mix a slow-acting analogue of insulin, insulin degludec, with insulin aspart was an embodiment that represented an inventive advance in the art, even over the use of insulin degludec alone. He stated out that the skilled person, with knowledge that alternative slow-acting insulins (glargine and detemir) could not be combined with insulin aspart, would have no reason to believe that it would be possible to combine insulin degludec and insulin aspart in the manner disclosed in the patent.

19. The agent repeated the advantages arising from the use of the co-formulation

over the separate administration of the two mono-products, given that insulins required frequent (e.g. several times daily) self-administration by a diabetes patient. He noted that some injections were taken at home, others at work, on vacation, or in restaurants etc. Real world experience had shown that some patients using different products in combination, e.g. administration by injection from two different pen-like injectors, did sometimes mix-up the products or the individual dosages of each. On the other hand, when rapid- and slow-acting insulins were in the same formulation (as in the present case), the patient needed only one product, only a single injection was required, and the ratio of the rapid- to slow-acting insulins was fixed. The relative simplicity of such a single product with only one injection eliminated some of the mistakes that otherwise tended to occur for some patients. Finally, he cited one further advantage of the co-formulation, namely the need for less frequent blood glucose measurements, leading to less blood glucose sampling for the patient and less cost for blood glucose measurement strips which themselves constituted significantly to the treatment cost.

THE BASIC PATENT

20. The basic patent EP2107069 was filed on 22 July 2004 with an earliest priority date of 5 August 2003 and is entitled *"Novel insulin derivatives"*. Paragraph [0001] states that the invention relates to *"… novel human insulin derivatives which are soluble at physiological pH values and have a prolonged profile of action."* It further refers to *"… methods of providing such derivatives, to pharmaceutical compositions containing them, to a method of treating diabetes and hyperglycaemia using the insulin derivatives of the invention and to the use of such insulin derivatives in the treatment of diabetes and hyperglycaemia."* Paragraphs [0002] to [0013] review the prior art relating to long-acting insulin compositions and summarises the various problems associated with each of them.

21. Paragraph [0014] states the problem the invention is seeking to address as follows: - *"… there is still a need for insulins having a more prolonged profile of action than the insulin derivatives known up till now and which at the same time are soluble at physiological pH values and have a potency which is comparable to that of human insulin."* And in paragraph [0015]: - *"The present invention is based on the recognition that the overall hydrophobicity of an insulin derivative molecule plays an important role*

for the in vivo potency of the derivative."

22. Paragraphs [0016] to [0036] disclose the chemical structure of the insulin derivatives of the invention in different embodiments and specifically mention the parent insulin of these various derivatives as des(B30) human insulin. Paragraph [0037] lists a number of these derivatives, including insulin degludec.

23. Paragraphs [0039] to [0044] describe the use of these insulin derivatives in pharmaceutical compositions for the treatment of type 1 and type 2 diabetes and other conditions that cause hyperglycaemia in human patients. Paragraph [0045] specifically discloses using such insulin derivatives in mixture with a rapid-acting insulin or insulin analogue for treating hyperglycaemic patients. Paragraph [0065] refers to specific rapid-acting insulin analogues in EP patent publications EP214826 (Novo Nordisk A/S), EP375437 (Novo Nordisk A/S) and EP383472 (Eli Lilly & Co.).

24. Paragraphs [0075-0204] detail the preparation and synthesis of the insulin derivatives of the invention and paragraphs [0205-0219] describe the pharmacological studies carried out using these derivatives.

ANALYSIS

25. At the oral hearing on 23 November 2018 the applicant was represented by Cathal Lane and Martin Parsons – both from Tomkins. In addition to myself, Dolores Cassidy, the examiner who handled the case, and Fergal Brady were also in attendance.

26. The discussion at the hearing went over all the points raised both in the pre-hearing submission and the earlier communications between the examiner and the agent.

27. I brought up an issue not raised previously, namely the need to apply for an SPC for the combination product when, by way of the SPC already granted for insulin degludec, the applicant had obtained the maximum 15-year period of exclusivity as provided for in recital 9 of the SPC Regulation. The agent explained that there was no guarantee any future evolution of case law might not call into question the protection for

the combination provided by the SPC for the mono-product.

28. The objection raised by the examiner to the grant of this SPC request was directed at non-compliance with Article 3(c). She reached this conclusion on the basis that, in her opinion, it was insulin degludec on its own which represented the "core inventive advance" of the patent and, as such it, and it alone, satisfied Article 3(a). As insulin degludec had already been the subject of an earlier granted certificate it was not possible to grant another SPC for the combination of insulin degludec and insulin aspart in contravention of Article 3(c).

29. The interpretation of Article 3(a) has, and continues, to cause great difficulty for national intellectual property offices as may be seen by the diversity of national court decisions and from the number of referrals to the CJEU going as far back as 1997. In 2010 the first referral specifically related to combination products arose in the case C-322/10 *Medeva BV v Comptroller (Medeva)* and included one question about Article 3(a) relevant to the present case, namely: *"What is meant in Article 3(a) by "the product is protected by a basic patent in force" and what are the criteria for deciding this?"* The court answered that Article 3(a) precluded the grant of an SPC relating to active ingredients which were not specified in the wording of the claims of the basic patent. In the present case, however, this is not at issue since the combination of insulin degludec and insulin aspart is explicitly specified in claim 11.

30. The judgment in *Medeva* does have relevance in the present case because, in distinguishing for the first time between the *"extent of protection"* of the basic patent and its *"protective effect",* the court rejected the classic "infringement test" which had held sway up to that point. This was outlined in paragraph 70 of the Opinion of the Advocate General, namely: *"Nevertheless, the definition of the basic patent laid down in Article 1(c) of the Regulation requires that, in the application of that definition, regard is always had to the subject-matter of the patent in question, and not to its protective effects."*

31. Despite this clear rejection of the "infringement test" by the CJEU in *Medeva*, the uncertainty around the interpretation of Article 3(a) has continued. Several additional expressions such as *"a totally separate innovation"* in *Sanofi* and *"the subject matter of the invention covered by the patent"* in *Boehringer* have emerged from these judgments.

Furthermore, in paragraph 22 of *Sanofi* the CJEU repeats the language used by the judge in the UK referring court that *"… the key factor is whether the active ingredient or combination of active ingredients in question constitutes the core inventive advance embodied by the basic patent."*

32. From the case law of the CJEU it seems to be clear that the expression "product protected by a basic patent in force" within the meaning of Article 3(a) of the SPC Regulation refers to the rules governing the "extent of protection" and not the rules governing infringement. Paragraph 25 of *Medeva* sets forth clearly that, to be considered "protected by a basic patent" within the meaning of that provision, the active ingredients should be specified in the wording of the claims of that patent. However, the judgments in *Sanofi* and *Boehringer* indicate that "more is required" for the purposes of determining whether a *"product is protected by a basic patent in force"* and that it is necessary to take into account the *"core inventive advance of the patent"* or the *"subject matter of the invention covered by the patent."*

33. In this regard I find the conclusion in *Boehringer* especially relevant in this case given the clear statement by the CJEU in paragraph 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 469/3009, that active ingredient must constitute the subject-matter of the invention covered by that patent."* It was this reasoning that the examiner focussed on in her letter of 10 June 2016 when citing the court's answer to the question and applying it to the present case – see paragraphs 5 and 6 of this decision.

34. It was exactly this issue of "*the subject-matter of the invention covered by that patent"* that the CJEU addressed in more detail recently in *Teva*, as outlined in paragraph 43 therein: *"Accordingly, …, the claims cannot allow the holder of the basic patent to enjoy, by obtaining an SPC, protection which goes beyond that granted for the invention covered by that patent. Thus, for the purposes of the application of Article 3(a) of that regulation, the claims of the basic patent must be construed in the light of the limits of that invention, as it appears from the description and the drawings of that patent."* What the CJEU appears to be saying is that the delay in the commercial exploitation, upon which the Regulation itself is based, is to be compensated only for the part of the invention that makes up the core of the inventive step constituting the subject

matter of the basic patent.

35. The court went on to explicitly address the "subject matter" in paragraph 46: *"It follows from the above that the subject matter of the protection conferred by an SPC must be restricted to the technical specifications of the invention covered by the basic patent, such as claimed in that patent."*

36. With regard to the claims of the basic patent, the court stated in paragraph 47 *"…, the claims of a patent are to be interpreted from the perspective of a person skilled in the art and, therefore, the issue whether the product which is the subject of the SPC necessarily falls under the invention covered by that patent must be assessed from that perspective."*

37. In order to make this assessment the court then provided some further guidance in paragraph 48: *To that end, it is necessary to ascertain whether a person skilled in the art can understand without any doubt, on the basis of their general knowledge and in the light of the description and drawings of the invention in the basic patent, that the product to which the claims of the basic patent relate is a specification required for the solution of the technical problem disclosed by that patent."* And in paragraph 49: "*In the second place, having regard to the objective of Regulation No 469/2009, recalled in paragraph 39 above, for the purposes of assessing whether a product falls under the invention covered by a basic patent*, account *must be taken exclusively of the prior art at the filing date or priority date of that patent, such that the product must be specifically identifiable by a person skilled in the art in the light of all the information disclosed by that patent."*

38. Finally, in paragraph 57 the court formulated its answer to the question referred as follows: *"…, the answer to the question referred is that Article 3(a) of Regulation No 469/2009 must be interpreted as meaning that a product composed of several active ingredients with a combined effect is 'protected by a basic patent in force' within the meaning of that provision where, even if the combination of active ingredients of which that product is composed is not expressly mentioned in the claims of the basic patent, those claims relate necessarily and specifically to that combination. For that purpose, from the point of view of a person skilled in the art and on the basis of the prior art at the filing date or priority date of the basic patent:*

– *the combination of those active ingredients must necessarily, in the light of the description and drawings of that patent, fall under the invention covered by that patent, and*

– *each of those active ingredients must be specifically identifiable, in the light of all the information disclosed by that patent.*

39. This specific issue of the "*the subject-matter of the invention covered by that patent"* was also discussed in the judgment in the case 4b O 43/18 Merck Sharp & Dohme Corp., vs Hexal AG (*MSD*) before the Landgericht Dusseldorf in Germany and issued on 1 October 2018, and the following paragraph on page 22 of the English translation (first paragraph on page 21 in the original German version) is relevant to my analysis: *"Moreover, the Chamber feels that, besides the synergistic effect, other modes of action are conceivable for a combination of active ingredients which can form the core of the invention protected by the Basic Patent. A mode of action which helps reduce side effects and makes administration easier can absolutely constitute the core of the subject matter of the invention if it is different from the mode of action of the mono-active ingredient. But for that to happen, the Basic Patent must contain reliable indications at the priority date that prove that the combination of active ingredients will achieve this form of effect."*

40. As summarised previously, the invention disclosed in the basic patent is clearly and solely directed at novel human insulin derivatives which are soluble at physiological pH values, have a prolonged (i.e. slow-acting) profile of action, and are useful in the treatment of diabetes and hyperglycaemia. The invention is based on the recognition that the overall hydrophobicity of an insulin derivative molecule plays an important role for its potency *in vivo* and as such it is addressing the problems associated with long-acting insulin compositions as very clearly explained in paragraph [0006] and [0014] of the patent.

41. As also mentioned earlier, the agent quoted a comment from the American Diabetic Association in 2003 that another long-acting insulin, glargine, should not be mixed with other forms of insulin. This would indicate that the issue of combining long- and rapid acting insulins, as well as some of the problems associated with doing so, was

already known in the prior art. What the basic patent in this case does not include is any mention whatsoever of this problem i.e. that of providing a combination of a long- and rapid- acting insulin derivative that can be brought together in a co-formulation with positive benefits for a diabetes patient.

42. The agent quoted extensively from the 2014 *Dardano* publication to outline the specific problems faced in combining such long- and rapid acting compositions and to explain in detail how and why the co-formulation in Ryzodeg successfully overcame these problems. I note that *Dardano* references the European Medicines Agency (EMA) report: *Ryzodeg (insulin degludec/insulin aspart): EU Summary of Product Characteristics: 2013.* This publication appears to be the first to disclose the pharmacological properties of the co-formulation. The basic patent is completely silent in this regard i.e. there is no information to suggest that the co-formulation of claim 11 will achieve the desired result. As the EMA report was published about 9 years after the priority date of the basic patent (5 August 2003), this might account for the fact that the basic patent contains no reliable indications that the combination of active ingredients in Ryzodeg was likely to achieve the desired effect.

43. Furthermore, I note that, in addition to a claim protecting the specific combination of insulin degludec and insulin aspart, there is also a claim – claim 10 – to a combination of <u>any</u> of the novel insulin derivatives of claim 1 with <u>any</u> rapid-acting insulin analogue. This would appear to teach away from the suggestion of it being already known that only the degludec and the aspart could be successfully combined.

44. Therefore, if I apply the two-part "test" formulated by the court in *Teva*, I conclude that both active ingredients in the co-formulation are "… *specifically identifiable, in the light of all the information disclosed by that patent."* But for the other part of the test I am convinced that the co-formulation does not *"in the light of the description and drawings of that patent, fall under the invention covered by that patent"* for the reasons outlined above.

45. Accordingly, I believe that the product in this case, i.e. the combination of insulin degludec and insulin aspart is not protected as such by a basic patent in force as required by Article 3(a) of the SPC Regulation.

DECISION

The request for the grant of a Supplementary Protection Certificate 2013/035 by Novo Nordisk A/S for the product *"Combination of insulin degludec and insulin aspart in all its forms as they are protected by the basic patent"* does not meet the requirements of because this product is not protected as such by a basic patent in force. The request is therefore rejected under Article 10(2) of the SPC Regulation.

Dr. Michael Lydon - Hearing Officer
14 January 2019