Decision in Respect of a Request by AstraZeneca AB for the Grant of a Supplementary Protection Certificate (SPC) No. 2014/038

INTRODUCTION

1. This decision concerns a request for the grant of an SPC No. 2014/038 filed on 7 July 2014 on behalf of AstraZeneca AB (the applicant) by FRKelly (the agent) for the product: *"A combination of dapagliflozin or a pharmaceutically acceptable salt thereof and metformin or a pharmaceutically acceptable salt thereof".*

2. The basic patent cited in support of the SPC request was European Patent EP1506211 with the title *"C-aryl glucoside SGLT2 inhibitors and method".*

3. The agent also submitted a copy of the Commission Decision granting the European marketing authorisation (MA) and the corresponding annexes including the summary of product characteristics (SmPC).

4. The legislation governing SPCs is Council Regulation (EEC) No. 1768/92 - *"the supplementary protection certificate for medicinal products"* - and as it was subsequently amended by the Paediatric Regulation and codified as Regulation (EC) 469/2009 – hereinafter the *'SPC Regulation'*.

5. The examiner wrote to the agent on 24 June 2016 to state that the request did not comply with the requirements of Article 3(a) and (c) of the SPC Regulation. She pointed out that an SPC (No. 2013/013) based on the same patent had already been granted to the applicant for the product *"Dapagliflozin and pharmaceutically acceptable salts thereof".* She queried whether it was possible to obtain more than one SPC on the basis of the same patent, albeit with different MAs, and she cited two CJEU rulings on this issue. Firstly, in the case C-443/12 (*Sanofi*) the Court ruled: - *"… on the basis of a patent protecting an innovative active ingredient and a marketing authorisation for a medicinal product containing that ingredient as the single active ingredient, the holder of that patent has already obtained a supplementary protection certificate for that active ingredient …, Article 3(c) … must be interpreted as precluding that patent holder from obtaining – on the basis of that same patent but a subsequent marketing authorisation for a different*

medicinal product containing that active ingredient in conjunction with another active ingredient which is not protected as such by the patent – a second supplementary protection certificate relating to that combination … ."

6. Likewise she noted in the case C-577/13 (*Boehringer*) that the Court ruled: - *"Article 3(a) and (c) …, 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."* In the light of these judgements she concluded that the present SPC request did not comply with the requirements of Article 3(a) and (c) of the Regulation.

7. The agent responded on 18 October 2016 to argue that the patent in the present case differed to that in *Boehringer* because: - "*the combination of 'dapagliflozin and metformin' represented a distinct invention from the dapagliflozin monoproduct*". He claimed that *dapagliflozin* was not the "sole subject-matter" of the basic patent and reminded the examiner that it was possible to obtain more than one SPC on the basis of the same patent, as indicated in *Sanofi: - "…, it is possible, … , to obtain several SPCs in relation to each of those different products, provided, inter alia, that each of those products is 'protected' as such by that 'basic patent' within the meaning of Article 3(a)".* He quoted the CJEU decision in the case C-484/12 (*Georgetown)* as further support for his contention that it was possible to obtain more than one SPC from the same patent.

8. The agent also noted that the Court's ruling in *Sanofi* had included a finding that the combination product at issue was not protected as such by the basic patent. This was in contrast to the present case where there was at least one claim directed to a specifically identified combination of a C-aryl glucoside SGLT2 inhibitor (defined in claim 1 of the basic patent as the compound of formula I i.e. *dapagliflozin*) and *metformin* (the first anti-diabetic agent identified in the list in claim 7). He claimed that the SPC should be granted because the second active ingredient, *metformin,* was specifically '*protected as such by the patent*', and repeated that this was in contrast in contrast to the facts in *Sanofi* where the patent only contained a claim to a composition containing a first active, *irbesartan,* in combination

with a non-specific diuretic. He referred to paragraph 54 of the patent which indicated a compound, such as *dapagliflozin*, in combination with another anti-diabetic agent, notably *metformin*, would act synergistically – this he said represented a yet further distinction over the basic patent in *Sanofi*.

9. The examiner replied on 7 February 2020 to state she was not persuaded by the argument that the combination represented a distinct invention over and beyond that of the monotherapy. She described the statement in paragraph 54 of the patent regarding such a combination as merely professing a belief that it might produce a synergistic effect and pointed out that there was no other information in the patent to back this up. She referred to paragraphs 49 and 50 from the CJEU judgment in the more recent case C-121/17 (*Teva)* to argue that it would be obvious for a skilled person to combine the new compound of formula I of the patent with existing active compounds for the treatment of diabetes. She restated her opinion that the combination of *dapagliflozin* and *metformin* could not be regarded as a new invention in itself. She also drew the agent's attention to a recent Irish High Court judgment in the case *Merck Sharp & Dohme Corp v Clonmel Healthcare Limited [2019] IEHC 814*, and in particular to paragraphs 69 - 95 where the judge had summarised the test set out by the CJEU in *Teva*. In conclusion, she confirmed her objection and her intention to reject the SPC request.

10. The agent replied and requested that a hearing be held in the case and a date was subsequently agreed upon. However, before this could take place, he submitted a request for a stay of proceedings pending a ruling from the CJEU in the case C-650/17 *(Royalty Pharma)*. He explained that this ruling would be relevant to the examination of the outstanding objections in the present SPC request since the three questions referred were directly concerned with the interpretation of the requirements of Article 3(a).

11. This request was agreed to by the examiner and the case was put on hold. In June 2020 she contacted the agent to inform him that the CJEU had issued its judgment in *Royalty Pharma* and invited him to make a further submission on foot of this. The agent replied in July 2020 to maintain his request for a re-scheduled hearing, and he also included a detailed written pre-hearing submission.

12. Whilst the agent had repeated a preference for a face-to-face hearing and that this might take place in the autumn of 2020, it proved to be impossible due to the ongoing restrictions brought about by the pandemic. Finally, the examiner wrote to the agent in January 2021 and proposed that it be conducted by way of videoconferencing. This was agreed and a date of 16 April 2021 was set for the hearing.

13. At the hearing, the applicant was represented by Luke Maishman and Donal Kelly (both of FRKelly). In addition to myself as Hearing Officer, Dolores Cassidy (who examined the case) also attended.

ANALYSIS

14. The objection raised by the examiner was directed at non-compliance with Articles 3(a) and 3(c) of the *SPC Regulation* since a certificate (SPC No. 2013/013) had already granted for the mono-product *"dapagliflozin"* based on the same patent. This earlier SPC will enter into force on 15 May 2023 upon expiry of the basic patent and will itself expire on 13 November 2027 - thereby extending the protection afforded to the product by about 4½ years. The examiner noted that the issue of obtaining more than one SPC based on the same patent, albeit with different MAs, had been ruled on by the CJEU in the cases C-443/12 (*Sanofi)* and C-577/13 (*Boehringer)* and cited these judgments to support her objection.

15. In *Boehringer* the CJEU appeared to re-emphasise the need for balance between the interests of the pharmaceutical industry and those of public health. It ruled that, even though in that particular case each of the active ingredients and the specific combination were expressly mentioned in the claims, this in itself was not sufficient to satisfy the requirements of Article 3(a) because the second active ingredient was not the "*subject-matter of the invention"* covered by the patent.

16. An earlier CJEU referral specifically related to combination products was made in the case C-322/10 *(Medeva)*. The first question was: - *"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 expression *"product protected by a basic patent in force"* within the meaning of Article 3(a) was adjudged by the Court to refer to the rules governing the "*extent of*

protection" and not to those governing the *"protective effects*" of the patent. This point was mentioned in paragraph 69 of the Attorney General's Opinion: - *"The decisive consideration in that context is the fact that the definition of the basic patent in Article 1(c) of Regulation No 469/2009 takes as its basis the subject-matter of the patent, and not its protective effect."* And again in paragraph 70: - *"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."*

17. However, although the Court in *Medeva* stated that, to be considered *"protected by a basic patent"*, the active ingredients must be specified in the wording of the patent claims, their rulings in both *Sanofi* and *Boehringer* had indicated that *"more is required"* for the purposes of fully meeting the requirements of Article 3(a). The point was highlighted by the CJEU at paragraph 38 in *Boehringer*: - *"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 issue of "*the subject-matter of the invention covered by that patent*" that the examiner focussed on in her letter of 24 June 2016 in her objection to the SPC request .

18. The case presented by the agent was based upon the pre-hearing written submission. He began with a brief summary of the case to date and then set out in detail his arguments in support of the SPC request. This included an analysis of the more recent CJEU, UK and Irish case law since the agent's response to the examiner in October 2016. The agent briefly reiterated his arguments made around the CJEU rulings in the *Sanofi* and *Boehringer* cases and went on to explain his understanding of the ruling in the *Teva* case. The agent noted that the CJEU had now set out a specific test for determining compliance with Article 3(a) of the SPC Regulation and emphasised it had also appeared to expressly discount the requirement for a "*core inventive advance*" which had been proposed to it by the referring UK High Court.

19. In *Teva,* the agent noted the CJEU's conclusion that the subject matter of protection conferred by the SPC must be restricted to the *"technical specifications of the invention covered by the basic patent, such as claimed in that patent".* He cited the test

as set out by the Court in its final ruling: - *"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."*

20. The agent explained that, upon the case's return to the UK High Court, the judge had interpreted the test in *Teva* (at paragraph 15) to require that the product must embody "*the technical contribution made by the patent"* – see *Teva UK Limited & Ors v Gilead Sciences, Inc [2018] EWHC 2416 (Pat)*. The agent summarised the outcome of the case before the UK Court of Appeal (*Teva UK Limited & Ors v Gilead Sciences, Inc [2019] EWCA Civ 2272)* and noted that the Court had also rejected the "*core inventive advance"* test. In doing so he claimed it had echoed the AG's Opinion in the joined cases *C-650/17* and *C-650/18 (Royalty Pharma* and *Sandoz).* The agent highlighted the Appeal Court's statement, in relation to the first limb of the *Teva* test, in paragraph 82, the *"express mention of the active ingredient in the claim is enough"* to satisfy the requirement for the combination to *"fall under the invention covered by the patent".*

21. The agent also commented on the two most recent cases before the Irish High Court in October and November 2019, respectively in *Gilead v Teva [2019] IEHC* 683 and in Merck *Sharp & Dohme Corp v Clonmel Healthcare Limited [2019] IEHC 814.* In *Gilead,* he highlighted parts of the judge's summary of the *Teva* test in paragraph 141: - *(a) Whether the combination … necessarily, in the light of the description and drawings of the patent, falls under the invention covered by the … patent".* And: - *(b) "Whether each of those active ingredients are specifically identifiable, in the light of all of the information disclosed by the patent".* In *Merck Sharp & Dohme* he underlined the analysis in

paragraphs 90 and 95 where the judge, in applying the first limb of the *Teva* test, stated: - "… *it is significant whether or not the combination product was new and inventive and had been "shown to be useful"* at the priority date, and the agent noted the judge's finding that the combination itself had failed this part of the test.

22. In summarising these Irish cases, the agent commented that both judgments had been issued before the CJEU's ruling in the *Royalty Pharma* case*.* He emphasised that the *Royalty Pharma* judgment was particularly significant in the present case because: - (a) the Court had underlined "*the key role played by the claims"* in determining whether a product was protected by a basic patent, and (b) it had sought to clarify that the test set down in *Teva* was only necessary *"… where that product is not expressly mentioned in the claims of that patent, …".* However, I have noted the comment of the judge in the last paragraph of the *Merck Sharp & Dohme* decision: - "*Finally, it should be noted that neither side made any application to defer this judgment pending publication of the decision of the CJEU in Royalty Pharma."*

23. Whilst the agent pointed out that no other Irish Court decisions had issued since the *Royalty Pharma* judgment, that situation has changed as both High Court decisions were appealed, and judgments were issued by the Court of Appeal in February 2021, namely, *Gilead v Teva [2021] IECA 22* (*Gilead)* and *Merck Sharp & Dohme Corp v Clonmel Healthcare Limited [2021] IECA 54 (MSD)*.

24. Before turning to these recent Appeal Court cases, it is worthwhile looking at the original *MSD* case before the High Court in which the judge gave a summary of his application of the *Teva* test in the earlier *Gilead* case (see paragraphs 65 – 95). The *MSD* case is more relevant to the analysis of the present SPC request since it also involved a combination of active ingredients which was explicitly claimed in the basic patent – this was not the case in *Gilead.* With regard to the first part of the *Teva* test, the High Court judge concluded: - *"… the approach taken by the CJEU is invention focussed rather than claims focussed. While the claims are important, a product will not be considered to be protected by a basic patent for the purposes of Article 3(a) unless it falls within the ambit of an invention the subject of that patent."* In considering the second part of the *Teva* test, he repeated that, 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."*

25. The judge referred to his earlier decision in *Gilead* to repeat his view that it would be "*unsafe to consider*" that the CJEU had intended to lay down a "*core inventive advance*" test. Rather he stated that such cases should be decided by deferring to the actual language used by the CJEU, i.e. by reference to whether the product in question fell within the ambit of the *"invention covered by [the] patent".* The judge concluded that the combination in question was not an invention covered by the patent on the basis of his reading of the patent and of the other evidence put before the Court and in his decision, he emphasised that: - *"For the patent to protect the combination, the combination must itself be an invention covered by the patent."*

26. In the Appeal Court *Merck, Sharp & Dohme* repeated its contention that the test in *Teva* should only be applied to cases where one of the active ingredients was not expressly mentioned in the claims of the basic patent, and it quoted from the CJEU's decision in *Royalty Pharma* in support of this. The Appeal Court judge noted paragraph 74 of the AG's Opinion in *Teva*: - *"… merely because a substance might fall within the protection of the claims of a patent under Article 69 of the EPC and the Protocol on its interpretation and the provisions of relevant national law … does not necessarily imply that that substance is a product protected by a patent within the meaning of Article 3(a)".* The judge also noted the AG's opinion at paragraph 49 in *Royalty Pharma* where he appeared to dismiss as irrelevant any distinction between a product consisting of a single active ingredient and of a combination of active ingredients: -*"What matters instead is that, as the Court said at paragraph 57 and the operative part of the judgment [in Teva], where the ingredient(s) of the product is or, as the case may be, are not expressly mentioned in the claims of the basic patent, 'those claims relate necessarily and specifically' either to that active ingredient or, in the case of a multiplicity of active ingredients to that combination. This is so even if the Court was in terms considering only the position with regard to several active ingredients."*

27. At this point in his decision the Appeal Court judge analysed how the UK Courts had subsequently dealt with the *Teva* case upon receipt of the CJEU ruling. In the referral back to the UK High Court, the judge ruled that the SPC granted to *Gilead* in respect of

the combination product was invalid, whereupon *Gilead* submitted an appeal so that the case went before the UK Court of Appeal - *Teva UK Ltd. & Ors. v. Gilead Sciences Inc. [2019] EWCA Civ. 2272*). The UK Appeal Court judge stated that the expression *"fall under the invention covered by the patent"* ruled out any consideration of the *"inventive advance"* in the patent since the CJEU itself had rejected the core inventive advance test. He was of the view that paragraph 37 in *Teva* meant that express mention of the active ingredient in the claim was sufficient to satisfy the requirements of Article 3(a).

28. However, the Irish Appeal Court judge stated that she read this part of the CJEU's judgment in the opposite sense. In other words she took this to mean that the CJEU was effectively establishing a *"fall under the invention covered by the patent test*". In so doing, she believed that the Court was requiring the national court to assess the invention of the patent by reference to the description and drawings of the basic patent. Whilst the Irish judge was agreeing with the UK Appeal Court judge on the point that express mention in a claim says nothing about whether the added ingredient formed part of the inventive advance, she was disagreeing with him in her conclusion that the phrase "*falling under the invention covered by the patent*" prohibits the national court from engaging in an assessment of the invention covered by the patent.

29. In his conclusion on Article 3(a) in paragraph 82, the Appeal Court judge emphasised her view that the CJEU ruling in *Teva* did require the national court to assess whether the product, the subject of an SPC, falls under the invention covered by the basic patent. She also confirmed his endorsement of the trial judge's clear rejection of *Merck, Sharp & Dohme's* argument and his interpretation of *Royalty Pharma* that it was sufficient for the purposes of Article 3(a) that the two active ingredients were expressly mentioned in the claims of the patent and that no assessment of the invention of the patent was either required or permitted. She repeated the trial judge's comment on this question: - *"… the addition of an existing compound to a novel compound cannot, without more, make the combination an invention in itself. If that was all that was required, it would mean that an SPC would automatically be available for any combination product containing a combination of a novel product disclosed in a patent and a pre-existing product available off the shelf."* The Appeal Court judge confirmed that the High Court judge was correct in both his approach and his assessment under Article 3(a), and the appeal was refused.

30. Given the above analysis of the relevant case law and the arguments put forward by the agent, I now turn back to the present case. The title of the basic patent is "C-aryl glucoside SGLT2 inhibitors and method". The "Field of the invention" is described as follows: - *"The invention relates to C-aryl glucosides which are inhibitors of sodium dependent glucose transporters found in the intestine and kidney (SGLT2) and to a method of treating diabetes, especially type II diabetes, as well as a number of other diseases, employing such C-aryl glucosides alone or in combination with one, two or more type antidiabetic agents and/or one, two or more type therapeutic agents such as hypolipidemic agents."*

31. Type II diabetes is characterised by hyperglycaemia due to excessive glucose production in the liver and to peripheral insulin resistance. Normalization of plasma glucose in patients is well-known both to improve insulin action and to offset the development of diabetic complications. The *SGLT2* protein stops glucose in the blood from being passed out into the urine. By inhibiting the action of SGLT2, C-aryl glucosides cause the kidneys to pass out more glucose in the urine, reducing the levels of glucose in the blood and delaying the development of diabetic complications.

32. The invention discloses in claim 1 a particular compound of this C-aryl glucoside type (the compound of formula I), compositions employing this compound and methods of using it in the treatment of diabetes, either alone or in combination with other antidiabetic and/or hypolipidemic agents. The specific combination of *dapagliflozin* and *metformin* is claimed in claim 7. A process for preparing a particular C-aryl glucoside compound (the compound of formula I - *dapagliflozin*) is exemplified and fully described in the description in paragraphs [0021]–[0049].

33. Paragraph [0054] contains a statement that the combination of *dapagliflozin* with one or more other antidiabetic agents *"is believed"* to produce antihyperglycemic results greater than that possible from each of these medicaments alone and greater than the combined additive antihyperglycemic effects produced by these medicaments. The language used here appears very speculative indeed in nature with no evidence cited from research literature or experimental studies to support this statement. Moreover, in *Section 5.1 'Pharmacodynamic properties'* of the EMA Summary of Product Characteristics (SmPC) document, the medicinal product, Xigduo *(i.e. dapagliflozin* and *metformin)*, is

described as combining two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action, to improve glycaemic control in diabetic patients. This further suggests to me that the effect of the combination is additive rather than synergistic. It would appear that the only benefit of using the combination of these two active ingredients is one of improving adherence to the prescribed dosage regime by reducing the burden of multiple tablet administration. When this issue was raised at the hearing, the agent mentioned that such a statement was plausible, but he was unable to offer up any evidence which countered the statement in the SmPC document.

34. The description goes on at length to recite a very extensive list of agents which may be used in combination with *dapagliflozin*. These include other antidiabetic or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents having a mechanism of action different from SGLT2 inhibition such as biguanides, sulfonyl ureas, glucosidase inhibitors, etc. The patent also lists other types of more general therapeutic agents which may be used in combination with *dapagliflozin*. These include anti-obesity agents, antihypertensive agents, antiplatelet agents, anti-atherosclerotic agents and/or lipid lowering agents and finally it lists agents for treating complications of diabetes such as PKG and/or AGE inhibitors.

35. Paragraph [0055] states that the other antidiabetic agent may be an oral anti-hyperglycaemic agent preferably a biguanide such as *metformin* or *phenformin*. It should be noted that *metformin* was the first biguanide to be discovered in the 1920s and still remains today the most widely used medication for the treatment of type 2 diabetes. Likewise, *phenformin* is another well-known biguanide and it was developed in the 1950's. *Metformin* is mentioned again in paragraph [0065] but again only in a long list of other possible active ingredients for using in combination with *dapagliflozin.*

36. The statement by the CJEU in paragraph 41 of *Sanofi* is relevant: - "… *the basic objective of Regulation No 469/2009 is to compensate for the delay to the marketing of what constitutes the core inventive advance that is the subject of the basic patent, … . In the light of the need, referred to in recital 10 in the preamble to that regulation, to take into account all the interests at stake, including those of public health, if it were accepted that all subsequent marketing of that active ingredient in conjunction with an unlimited number of other active ingredients, not protected as such by the basic patent but simply referred*

to in the wording of the claims of the patent in general terms, such as, in the case of the patent in the main proceedings, 'beta-blocking compound', 'calcium antagonist', 'diuretic', 'non-steroidal anti-inflammatory' or 'tranquilizer', conferred entitlement to multiple SPCs, that would be contrary to the requirement to balance the interests of the pharmaceutical industry and those of public health as regards the encouragement of research within the European Union by the use of SPCs." As mentioned in paragraph 5 of this decision, the applicant has already been granted an SPC for the novel active ingredient, *dapagliflozin.*

37. In light of the above, I have come to the conclusion that the product in this case, the combination of *dapagliflozin* and *metformin*, does not *"fall under the invention covered by the patent"* - in other words, the product of the SPC request is not protected as such by a basic patent in force as required by Article 3(a) of the SPC Regulation. Furthermore, since the product *dapagliflozin* has already been the subject of a granted certificate, the SPC request does not meet the requirements of Article 3(c).

DECISION

I have concluded that the product named in this SPC request, the combination of *"dapagliflozin or a pharmaceutically acceptable salt thereof and metformin or a pharmaceutically acceptable salt thereof"* is not protected by a basic patent in force as required by Article 3 (a) of the SPC Regulation – it is only the *dapagliflozin* which is protected. Moreover, the SPC request also does not meet the requirements of Article 3(c) because the product *dapagliflozin* itself has already been the subject of a granted certificate. The request is therefore rejected under Article 10(2) of the SPC Regulation.

Dr. Michael Lydon
Hearing Officer
21 July 2021