Decision in Respect of a Request by Merck Sharp & Dohme Corp. for the Grant of a Supplementary Protection Certificate (SPC) No. 2014/050

INTRODUCTION

1. This decision concerns a request filed on behalf of Merck Sharp & Dohme Corp. ('MSD' – the applicant) by Tomkins & Co. (the agent) for the grant of an SPC No. 2014/050 filed on 11 September 2014 for a product (Viazet) with the product identity: *"Ezetimibe and rosuvastatin or pharmaceutically acceptable salts thereof, including rosuvastatin as a zinc salt"*. The basic patent cited in support of the request was European Patent EP0720599 with the title *"Hydroxy-substituted azetidinone compounds useful as hypocholesterolemic agents"*. In relation to this patent, the applicant stated that the product was protected in the following manner: *"Viazet is covered by claims 9 and 16, insofar as the latter is dependent on claim 9."*

2. In support of the request, the agent submitted additional documentation in the form of granted marketing authorisations (MAs) to Egis Pharmaceuticals PLC for three different formulations of *Viazet* (10mg/10mg; 20mg/10mg; 40mg/10mg):- (1) Copies of the Norwegian decisions of 24 July 2014 issued by Statens Legemiddelverk (Norwegian Medicines Agency); (2) Copies of the Hungarian decisions of 29 July 2014 issued by OGYÉI (Országos Gyógyszerészeti Intézet - National Institute of Pharmacy and Nutrition); and (3) Copies of the Irish decisions of 8 August 2014 issued by HPRA (Health Products Regulatory Authority). In each case, copies of the corresponding "Summary of Product Characteristics" document were also submitted.

3. The legislation under which such SPCs are granted is Council Regulation (EEC) No. 1768/92 concerning *"the supplementary protection certificate for medicinal products"* and as subsequently amended by the Paediatric Regulation to provide for an SPC extension and codified as Regulation (EC) 469/2009 – hereinafter the 'SPC Regulation'.

4. The examiner wrote to the agent on 26 November 2014 and stated that the SPC request did not comply with Article 3(c) of the SPC Regulation on the grounds that *"… an SPC has already been granted (to the same applicant) for "Ezetimibe or a*

pharmaceutically acceptable salt thereof", based on the same basic patent. (See SPC 2003/014)".

5. The examiner drew the agent's attention to paragraph 43 of a judgment from the Court of Justice of the European Union (CJEU) in *Sanofi*, which she held to be relevant to the present application: - *"… the answer to the second question referred is that, in circumstances such as those in the main proceedings, where, on the basis of a patent protecting an innovative active ingredient and 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 entitling him to oppose the use of that active ingredient, either alone or in combination with other active ingredients, Article 3(c) 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 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 of active ingredients."*

6. The examiner also referred to paragraph 30 of the same judgment in which the issue of multiple marketing authorisations had been raised in relation to the "core inventive advance of that patent": - "*However, in circumstances such as those in the main proceedings, even if the condition laid down in Article 3(a) of Regulation No 469/2009 were satisfied, for the purpose of the application of Article 3(c) of that regulation, it cannot be accepted that the holder of a basic patent in force may obtain a new SPC, potentially for a longer period of protection, each time he places on the market in a Member State a medicinal product containing, on the one hand, the principle active ingredient, protected as such by the holder's basic patent and constituting, according to the statements of the referring court, the core inventive advance of that patent, and, on the other, another active ingredient which is not protected as such by that patent."*

7. She went on to cite paragraph 42 in connection with the possibility of obtaining an SPC for a combination product, provided that combination was the subject of a patent in

its own right: - "*It follows that, in such a situation, Article 3(c) of Regulation No 469/2009 precludes a patent holder from obtaining, on the basis of one and the same basic patent, more than one SPC in connection with irbesartan, since such SPCs would in fact be connected, wholly or in part, with the same product (see, to that effect, with regard to plant protection products, Case C-258/99 BASF [2001] ECR I 3643, paragraphs 24 and 27). On the other hand, if a combination consisting of an innovative active ingredient in respect of which an SPC has already been granted and another active ingredient, which is not protected as such by the patent in question, is the subject of a new basic patent within the meaning of Article 1(c) of that regulation, the new patent could, in so far as it covered a totally separate innovation, confer entitlement to an SPC for that new combination that is subsequently placed on the market."*

8. Referring to the earlier granted SPC for ezetimibe, the examiner stated that she regarded this as constituting the 'core inventive advance' of the basic patent. Although she conceded that the patent did disclose the use of such hypocholesterolemic compounds as ezetimibe in combination with a cholesterol biosynthesis inhibitor (such as rosuvastatin), she was of the opinion that the rosuvastatin element was not protected as such by the basic patent and accordingly she proposed to reject the request.

9. On 21 May 2015 the agent responded to these objections by arguing that the facts of the *Sanofi* case were distinct from those in the present SPC case. In particular, she noted that the CJEU had determined that the invention disclosed in the basic patent in *Sanofi* related only to the irbesartan component (an RAS inhibitor). She explained that this conclusion had been reached on the basis that the diuretic hydrochlorothiazide, with which the irbesartan was in combination, was not only extremely well known, but that both classes of active ingredients included (i.e. RAS inhibitors and diuretics) were already well known in combination in the prior art.

10. In the present case the agent pointed out that ezetimibe fell within a group of "cholesterol lowering agents", whilst rosuvastatin belonged to a group known as "HMG-CoA reductase inhibitors". She explained that combinations of these two groups of compounds had been neither approved nor been on the market prior to the filing date of the basic patent. Unlike the situation in *Sanofi*, she argued that it was not known that cholesterol lowering agents could be administered alone as well as in combination with

HMG-CoA reductase inhibitors. She concluded that both ezetimibe on its own, and in combination with HMG-CoA reductase inhibitors such as rosuvastatin, constituted *"two separate and distinct inventive advances of the patent."*

11. On 18 January 2017 the examiner replied by rejecting the arguments made by the agent and restated her intention to reject the SPC request. On 24 January 2017 the agent formally requested a hearing and this was arranged for 11 April 2017. Prior to the hearing the agent filed a submission on 30 March 2017 outlining the arguments to be presented at the hearing.

THE BASIC PATENT

12. The basic patent EP 0720599 is entitled "Hydroxy-substituted azetidinone compounds useful as hypocholesterolemic agents" and the description states in paragraph [0001] that the invention relates to *"… hydroxy-substituted azetidinones useful as hypocholesterolemic agents in the treatment and prevention of atherosclerosis, and to the combination of a hydroxy-substituted azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis."*

13. Paragraph [0004] reviews the prior art relating to several azetidinones summarizing their usefulness in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in the arterial walls of mammals.

14. Paragraphs [0006] and [0007] outline how the regulation of cholesterol levels in humans and animals involves the control of dietary cholesterol and the modulation of cholesterol biosynthesis, bile acid biosynthesis and the catabolism of the cholesterol-containing plasma lipoproteins.

15. In paragraph [0008] the inhibition of cholesterol biosynthesis through the use of a HMG CoA reductase inhibitor and its efficacy in reducing plasma cholesterol and thereby reducing atherosclerosis is referenced. A combination therapy of a HMG CoA reductase inhibitor and a bile acid sequestrant is also highlighted as being more effective in treating patients with high cholesterol than either agent used alone as a monotherapy.

16. Paragraphs [0009] to [0013] disclose the chemical formula of the novel hypocholesterolemic compounds of the invention as well as listing some of the possible variants. Paragraphs [0016] and [0017] outline the use of an azetidinone cholesterol absorption inhibitor of the invention in combination with a cholesterol biosynthesis inhibitor to treat or prevent atherosclerosis, or to reduce plasma cholesterol levels.

17. Paragraph [0028] provides a list of cholesterol biosynthesis inhibitors for use in combination with the compounds of the invention. The list comprises HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981 (atorvastatin); HMG CoA synthetase inhibitors (e.g. L659,699); squalene synthesis inhibitors; squalene epoxidase inhibitors; and other cholesterol biosynthesis inhibitors such as DMP-565. Finally it states that the preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin. Paragraphs [0029] to [0060] describe methods for preparing the compounds of the invention.

18. Paragraph [0061] claims that the compounds of the invention lower serum lipid levels, in particular serum cholesterol levels, by inhibiting the intestinal absorption of cholesterol and by significantly reducing the formation of liver cholesteryl esters in animal models so that they are useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

19. Paragraphs [0062] and [0063] outline a procedure to illustrate the *in vivo* activity of the compounds of the invention by means of using hamsters given a controlled cholesterol diet to render them hyperlipidemic for subsequent dosage with the test compounds of the invention. Paragraph [0064] discusses the various pharmaceutical formulations and compositions of the compounds of the invention including acceptable excipients and additives.

20. Paragraph [0065] suggests daily dosage regimes for the compounds of the invention as a mono-therapy, and [0066] lists typical daily dosages for combination therapies where a hydroxy-substituted azetidinone is administered together with a cholesterol biosynthesis inhibitor. Dosages are given for both a combination with HMG CoA reductase inhibitors (statins) and also with other cholesterol biosynthesis inhibitors.

21. Paragraphs [0069] to [0126] provide detailed examples of how to prepare the compounds of the invention and paragraphs [0127] and [0128] exemplify some of the dosage forms of these compounds.

22. Finally paragraph [0133] gives a table illustrating *in vivo* data using the procedure outlined previously and showing the percent reduction in cholesterol esters for dosages of the 35 exemplified hydroxy-substituted azetidinones on the hyperlipidemic hamsters.

THE HEARING

23. At the oral hearing on 11 April 2017 the applicant was represented by Christina Gates and Con O'Connor (Tomkins & Co.), together with Deeba Hussein and James Horgan (Merck Sharp & Dohme Corp.). The examiner, who handled the case, Dolores Cassidy, and another examiner, Fergal Brady, were also in attendance.

24. Mr. Horgan referred to the *Sanofi* case and drew attention to paragraph 30 to remark that this case referred to the situation where the "other" active ingredient was not protected as such by the basic patent. He cited paragraph 29 to point out that several SPCs could be obtained on the basis of the same patent if they related to different products, and that each of these products were "protected" as such by that "basic patent". I confirmed to him that we did not require the second or "other" active ingredient to be protected as such, but rather we applied this requirement to the combination product and that the combination product itself covered a totally separate innovation.

25. Mr. Horgan went on to discuss the case *C-577/13, Actavis v Boehringer* ('*Boehringer*') and explained that the active ingredient "telmisartan" was clearly "the sole subject matter" of the invention - whereas in the current case he held that thereto be two inventive concepts present. He referred to the "ezetimibe plus atorvastatin" combination SPC application which had been granted under Article 3(c) after a hearing at the UKIPO. In arriving at a determination as to whether a second invention was present in such cases, Mr. Horgan proposed two criteria; (i) could the second invention have been filed separately, and (ii) would a dependent claim be independently valid over the independent claim covering the mono-component? He expressed the view that the combination product in the current case would satisfy both of these conditions.

26. In relation to *Sanofi*, Mr. Horgan was of the view that in paragraph 41 the CJEU was merely restating the language viz. "… the core inventive advance of that patent …" used by the referring court in the UK rather than endorsing it in any way. Likewise he referred to the term *"… the sole subject matter of the invention …"* in paragraph 26 of the Boehringer judgment which he also attributed to the referring court. In conclusion, he cited paragraph 50 of the Sanofi referral by the UK court – see *[2012] EWHC 2545 (Pat) Actavis v Sanofi* - and proposed that the appropriate test should be a test of the independent validity of the claim as mentioned therein.

27. In the same context Mr. Horgan cited paragraph 23 of the judgment in another UK case which has been referred to the CJEU – see *[2017] EWHC 13 (Pat) Teva et al. v Gilead* (*'Gilead'*). In this case he noted that the judge equated *"the inventive advance"* with *"the technical contribution"* in ruling on the independent validity of the claim to the combination product. Relating this to the current case, he argued that an SPC could be granted where there is a larger gap between the subject matter of a claim to the combination (i.e. ezetimibe plus a statin) and the prior art than between the single-active therapy (i.e. ezetimibe) and the prior art.

28. Mr. Horgan also referenced paragraph 34 of the judgment in the UK case *[2017] EWHC 539 (Pat) Teva et al. v Merck Sharp & Dohme* (*'MSD'*): - *"… On the other hand, it does not preclude the grant of an SPC for a combination of active ingredients, even if one of those active ingredients is protected by the basic patent and has already been the subject of an SPC, if the combination represents a distinct invention protected by the patent. If the combination is a distinct invention, it should not matter whether it is protected by the same patent or by a different patent."*

29. He went on to cite another reference to claim validity in paragraph 169: - *"…then Article 3(c) precluded the grant of the SPC in respect of the Product unless claim 16 of the Patent was independently valid over the claims which protected efavirenz and thus represented a distinct invention from the invention protected by those claims."*

30. However, he disagreed with the judge's assessment in paragraph 170: - *"Counsel for the Claimants submitted that it should be assumed for this purpose that the skilled*

person had efavirenz and its activity against HIV reverse transcriptase disclosed to them at the priority date. Although counsel for MSD took issue with this, I consider that it is correct. The question to be considered is not the conventional one of whether a claim is invalid over a particular item of prior art read in the light of the common general knowledge, but whether, given the invention of efavirenz, claim 16 represents a distinct invention such that it could in principle form the subject-matter of a separate patent." He expressed the view that this approach sought to introduce the concept of a "hypothetical disclosure" and that it would effectively "move the goalposts" in relation to prior art.

31. Ms. Hussein gave a brief review of the CJEU judgments in *Sanofi* and *Boehringer* and sought to relate them to the facts of the current case. In *Boehringer* she explained that telmisartan was one of a class of angiotensin antagonists which inhibit the renin-angiotensin system (RAS) pathway to reduce high bold pressure. Hydrochlorothiazide or HCTZ was a diuretic and was commonly known to be used in conjunction with RAS inhibitors. As a result it led to the finding in *Boehringer* that a combination of telmisartan with HCTZ was not inventive and she noted that it had been common ground that telmisartan was the sole subject-matter of the invention in that particular case. In the current case she explained that ezetimibe was not only a cholesterol biosynthesis inhibitor, but it was also to this day the only compound existing within its class. Rosuvastatin, on the other hand, was a statin, i.e. a HMG CoA reductase inhibitor, and she reminded me that such a combination could never have existed prior to the fling of the patent covering ezetimibe.

32. Ms. Hussein then went on to discuss the witness statement of Prof. Assmann which surveyed the treatment of coronary heart disease with lipid-lowering agents in the early 1990's as well as the relative efficacy and clinical benefits of ezetimibe monotherapies and ezetimibe/statin combination therapies. Prof. Assmann noted that the first MA for a statin, lovastatin, was granted in 1987 after it had been shown to lower plasma LDL cholesterol in humans and had been well tolerated in trials. He provided a table and list of the medicaments available at the beginning of the 1990s and stated that it was not common practice at that time to administer combinations of these medicaments to patients because of drug-drug interactions and the increased risk of side-effects.

33. Prof. Assman also referred to paragraph [0008] of the basic patent and the study

demonstrating the effectiveness of a combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant in patients. In his opinion this combination therapy only related to the treatment of a small number of patients with severe hypercholesterolemia. He then went on to describe studies from 2004 and 2005 which showed LDL cholesterol reductions of well over 50% using ezetimibe in combination with a statin and he mentioned the first clinical trial of such a combination in 2015.

34. After the hearing, the agent submitted three UK court decisions arising out of some discussion that had taken place regarding the level of disclosure in the patent about the combination product. This concerned the issue as to whether or not it was necessary to include in a patent specification practical examples, e.g. experimental results, to demonstrate that the invention would work in practice. Whilst these cases illustrate that it is not a bar to patentability if such practical examples are not included, I do not believe that they are of relevance in this case where I am seeking to make a determination from the standpoint of the SPC Regulation and the relevant case law.

ANALYSIS

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

36. The interpretation of Article 3(a) has, and continues, to cause great difficulty for national intellectual property offices as may be deduced from the number of referrals by national courts to the CJEU going as far back as the case *C-392/97 Farmitalia Carlo Erba Srl* in 1997. In that case the Court answered the question about Article 3(a) to the effect that the extent of patent protection may be determined only in the light of non-Community (i.e. national) rules which govern patents.

37. In 2010 a referral specifically related to combination products was made in the case

C-322/10 Medeva v Comptroller ('Medeva') and included five questions concerning Article 3(a). Only the first of these is 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. It also stated that if a patent claimed a combination of two active ingredients, but did not claim one of them individually, an SPC could not be granted for that active ingredient in isolation.

38. The judgment in *Medeva* is of particular relevance to the current case because, in distinguishing for the first time between the *"extent of protection"* of the basic patent and its *"protective effect",* the Court went on to reject the infringement test which had held sway up to this point. This had been outlined in paragraph 69 of the Opinion of the Advocate General, namely: *"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."* In a similar vein the Advocate General elaborated further on this 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."*

39. The *Sanofi* case, referred to earlier, also concerned the grant of an SPC for a combination product with the same question being posed under Article 3(a), as well as a further one: "In a situation in which multiple products are protected by a basic patent in force, does Article 3(c) preclude the proprietor of the patent being issued a certificate for each of the products protected?" The Court answered the second question by saying *"… an SPC for a combination product cannot be obtained where one active has already been subject of SPC and other active is not protected by the patent as such and unless the combination is a totally separate innovation."* It was in the light of this answer that the Court decided there was no need to address the Article 3(a) question.

40. In the *Boehringer* referral the relevant question was summarised as follows: - *"In the situation where a basic patent includes a claim to a product (A) and a further claim to that product in a combination of active ingredients (A + B) and an SPC has already been*

granted for the product (A), do Articles 3(a) and 3(c) preclude the grant of a second SPC for the combination (A+B)?" The Court answered to the effect that a patent protects a product *"as such"* under Articles 3(a) and 3(c) if it constitutes the subject matter of the invention covered by the patent. Furthermore, Articles 3(a) and 3(c) preclude the grant of a second SPC for the combination (A+B) if the first SPC for the product (A) relates to the sole subject matter of the invention.

41. As can be seen from the above brief overview and, despite the clear rejection of the "infringement test" by the CJEU in Medeva, the uncertainty around the interpretation of Article 3(a) has continued. As referred to previously, several new terms such as *"a totally separate innovation"* in *Sanofi* and *"the subject matter of the invention covered by the patent"* in *Boehringer* have emerged throughout the course of these judgments. Furthermore, in paragraph 22 of *Sanofi* the CJEU refers to the suggestion from the UK High Court of Justice 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."*

42. In the light of these judgments and the evolution of CJEU case law, I return to my earlier summary and analysis of the basic patent. As mentioned in paragraph 4, an SPC - 2003/014 - has already been granted for ezetimibe based on the same patent. This SPC was granted on 3 August 2005 to Schering Corporation (who merged with Merck & Co. in 2009) and has an expiry date of 16 October 2017. On the same date another SPC - 2005/001 - for the combination of ezetimibe and simvastatin, was granted to Schering based on the same patent and with an expiry date of 1 April 2019. At that time the examiner did not raise any objection to the grant of the SPC for the combination since simvastatin was specifically mentioned in claim 17 as one member of the group of HMG CoA reductase inhibitors. It should also be noted that the examination of that SPC predated the *Medeva* judgement by almost seven years.

43. At this point I note the comment in paragraph 41 of the case *C-443/12*, *Actavis v Sanofi* ('*Sanofi*'): - "*It should be recalled that the basic objective of Regulation No 469/2009 is to compensate for the delay to the marketing of what constitutes the core inventive advance that is the subject of the basic patent, namely, in the main proceedings, irbesartan. In the light of the need, referred to in recital 10 in the preamble*

to that regulation, to take into account all the interests at stake, including those of public health, if it were accepted that all subsequent marketing of that active ingredient in conjunction with an unlimited number of other active ingredients, not protected as such by the basic patent but simply referred to in the wording of the claims of the patent in general terms, such as, in the case of the patent in the main proceedings, 'beta-blocking compound', 'calcium antagonist', 'diuretic', 'non-steroidal anti-inflammatory' or 'tranquilizer', conferred entitlement to multiple SPCs, that would be contrary to the requirement to balance the interests of the pharmaceutical industry and those of public health as regards the encouragement of research within the European Union by the use of SPCs."

44. As summarised previously, the basic patent relates to hydroxy-substituted azetidinones useful as hypocholesterolemic agents in the treatment and prevention of atherosclerosis, and to the combination of a hydroxy-substituted azetidinone of the invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis. However, the description and claims are very largely focussed on the hydroxy-substituted azetidinones themselves and I feel this adds support to the examiner's assertion that it is these compounds alone that constitute the "subject matter of the invention" or the "core inventive advance" of the basic patent.

45. Furthermore, claim 16, upon which the applicant relies to satisfy the Controller that the product is protected by the basic patent, is much wider in scope than being merely limited to a combination of a hydroxy-substituted azetidinone and a HMG CoA reductase inhibitor. In its broadest terms, claim 16 also covers combinations of a hydroxy-substituted azetidinone with any of the group of squalene synthesis inhibitors, or with any of the group of squalene epoxidase inhibitors. The list of HMG CoA reductase inhibitors specifically mentioned in claim 17 does not even include rosuvastatin. In other words, no claim in the basic patent relates "implicitly but necessarily and specifically" (as expressed in paragraph 44 of case *C-493/12 Eli Lilly v HGS Inc*.) to the combination of ezetimibe and rosuvastatin.

46. As also mentioned previously, the basic patent describes an *in vivo* trial on hamsters to demonstrate the effectiveness of a number of the compounds of the invention as hypocholesterolemic agents. However, I note that a similar trial was not

conducted for any of the possible combinations contained in the relevant claims of the patent. Whilst I accept the agent's argument that such trials are not necessary from the point of view of guaranteeing protection for such combinations by the patent claims, nevertheless this casts doubt as to whether any of these combinations could be deemed to fall within the "subject matter" or the "core inventive advance" of the basic patent from the standpoint of the SPC Regulation.

47. Accordingly, I do not believe that the combination of ezetimibe and rosuvastatin is protected by a basic patent in force as required by Article 3 (a) of the SPC Regulation because this combination does not fall within "*the subject matter of the invention covered by the patent*" or does not represent *"a totally separate innovation"*. It is clear to me that it is only the ezetimibe which is protected.

48. Notwithstanding my above analysis and decision, I now propose to examine this request using a different approach, namely that proposed by Justice Arnold in the *Gilead* case mentioned by Mr. Horgan at the hearing and referred to in paragraph 27 previously.

49. This case was only referred to the CJEU in January 2017 and accordingly it has not yet been ruled upon. Justice Arnold poses the same question he had raised previously in *Sanofi*, namely: - *"What are the criteria for deciding whether "the product is protected by a basic patent in force" in Article 3(a) of the SPC Regulation?"* On this occasion, however, the judge offers the Court of Justice his own answer.

50. In paragraph 96 he sets the scene thus: - *"… As discussed above, it is now clear that it is not sufficient that dealings in the product would infringe a claim applying the Infringing Act Rules. It is also clear that it is necessary that the product falls within at least one claim of the basic patent applying the Extent of Protection Rules. In my view, however, it is not sufficient that the product falls within at least one claim of the basic patent applying the Extent of Protection Rules. As explained in paragraphs 39-43 above, and as the facts of the present case illustrate, the scope of protection test proves too much in this context. Accordingly, more is required."*

51. In paragraph 97 he explains his proposed answer: - *"What more is required? In my view, the answer is that the product must infringe because it contains an active*

ingredient, or a combination of active ingredients, which embodies the inventive advance (or technical contribution) of the basic patent. Where the product is a combination of active ingredients, the combination, as distinct from one of them, must embody the inventive advance of the basic patent. Thus in a case such as the present, where the inventive advance of the Patent consists generally of the compounds of formulae (1) and (1a), including specifically tenofovir disoproxil (TD), a medicinal product whose active ingredient is TD is protected by the Patent within the meaning of Article 3(a) because it embodies the inventive advance of the Patent. A medicinal product whose active ingredients are TD and another therapeutic agent such as emtricitabine in combination is not protected by the Patent within the meaning of Article 3(a) because the combination, as distinct from TD, does not embody the inventive advance of the Patent. This is not a question of the wording of the claims of the basic patent, which as discussed above can be manipulated by the patent attorney who drafts it, but of its substance. By contrast, if Gilead (or another inventor) were to obtain a patent for an invention consisting of a combination of TD and substance X which surprisingly had a synergistic effect in treating HIV, then a medicinal product whose active ingredients were TD and X would be protected by that patent since it would embody the inventive advance of that patent. In my view, this interpretation of Article 3(a) would accord with the object of the SPC Regulation, which is to encourage invention in the field of medicinal products by compensating inventors for the delay in exploiting their inventions due to the need to obtain regulatory approval, and not to confer unjustified monopolies"

52. If I apply the test proposed by Justice Arnold in the present case, then a claim to a combination product of ezetimibe and rosuvastatin has to be independently valid over any claim protecting ezetimibe, which has already been the subject of an SPC. In other words, the combination product must represent a distinct invention i.e. it must "embody the inventive advance of the basic patent." In order to make this assessment I should start from the position that ezetimibe and its inherent activity in lowering serum lipid levels, by inhibiting the intestinal absorption of cholesterol, effectively forms part of the prior art for the purpose of this determination.

53. Paragraph [0008] of the basic patent references a study demonstrating the effectiveness of a combination therapy of a known HMG CoA reductase inhibitor and a bile acid sequestrant as being more effective in human hyperlipidemic patients than

either agent as a monotherapy. While Prof. Assmann states that this study only concerned the treatment of a small number of patients with severe hypercholesterolemia, it does highlight the fact that combination therapies were known and had been reported upon at least as early as 1988 i.e. well before the priority date of the basic patent.

54. Paragraph [0028] of the patent provides a fairly comprehensive list of cholesterol biosynthesis inhibitors for use in combination with the compounds of the invention. The list comprises HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981 (atorvastatin); HMG CoA synthetase inhibitors (e.g. L659,699); squalene synthesis inhibitors; squalene epoxidase inhibitors; and other cholesterol biosynthesis inhibitors such as DMP-565. Finally it states that the preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin – I also note here that there is no mention of rosuvastatin.

55. Therefore, having the hydroxyl-substituted azetidinone compounds of the invention, there would not appear to be anything inventive in a claim protecting any one of these compounds in combination with a cholesterol biosyntheisis inhibitor such as rosuvastatin. Likewise there is no information provided in the basic patent that such a combination could be expected to produce a surprising or unexpected level of synergy in the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels.

56. In summary, by adopting the Justice Arnold's test I arrive at the same conclusion as in paragraph 47, namely, that the product in this case, i.e. the combination of ezetimibe and rosuvastatin, is not protected by a basic patent in force as required by Article 3 (a) of the SPC Regulation – it is only the ezetimibe which is protected.

DECISION

The request for the grant of a Supplementary Protection Certificate 2014/050 by Merck Sharp & Dohme Corp. for the product *"Ezetimibe and rosuvastatin or pharmaceutically acceptable salts thereof, including rosuvastatin as a zinc salt"* does not meet the

requirements of Article 3(c) because the product ezetimibe has already been the subject of a certificate. The request is therefore rejected under Article 10(2) of the SPC Regulation.

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Dr. Michael Lydon
Hearing Officer
3 August 2017