Grounds of Decision in Respect of a Request by Array BioPharma Inc. for the Grant of a Supplementary Protection Certificate (SPC) No. 2019/010

INTRODUCTION

1. This decision concerns a request for the grant of SPC application no. 2019/010 filed on 20 February 2019 on behalf of Array BioPharma Inc. by Hanna Moore + Curley in respect of the following product identity "C*ombination binimetinib and encorafenib, each in all forms protected by the basic patent*".

2. The legislation governing SPCs is Regulation (EC) No. 469/2009 *"concerning the supplementary protection certificate for medicinal products"* – hereinafter, the *"*SPC Regulation*".* The legislation governing the authorisation of medicinal products is Directive 2001/83/EC relating to "*medicinal products for human use"* – hereinafter, the *"*Medicinal Products Regulation*".*

3. Patent no. EP 2 727 918 *('Compounds and compositions as protein kinase inhibitors'*) was cited as the "basic patent" in support of the request, as required by Article 1(c) of the SPC Regulation.

4. Copies of the marketing authorisations (MAs) issued by the European Commission on 24 September 2018 respectively for *"MEKTOVI – binimetinib"* (EU/1/18/1315) and for *"BRAFTOVI – encorafenib"* (EU/1/18/1314) were also submitted.

5. In her accompanying letter, the agent highlighted the fact that the respective MAs for *binimetinib* and *encorafenib* were granted on the same date - 20 September 2018 - and that no separate single MA had been granted for a fixed-dose combination of the two active ingredients. However, she drew attention to the "*Summary of Product Characteristics*" (SmPC) document for both products, in which each respective single active ingredient was clearly indicated for therapeutic use with "in combination with" language relating to the other active. The agent remarked that there was nothing in the SPC regulation to expressly prohibit the granting of an SPC for a so-called "loose" combination in such circumstances.

6. The examiner responded on 1 April 2020 to state her opinion that a copy of a valid MA to place the combination medicinal product on the market had not been submitted. Specifically, she noted that protection was being sought for a *"combination of binimetinib and*

encorafenib, each in all forms protected by the basic patent", but that two separate MAs had been filed – one relating to "*binimetinib*" and the other to "*encorafenib*". She cited Article 2 of the *SPC Regulation* to argue that the product which was the subject of an SPC request could be a combination of active ingredients from a single medicinal product, but not a combination of active ingredients from multiple medicinal products.

7. Furthermore, the examiner also stated that the product identity cited on the SPC request form was not acceptable because the wording "*each in all forms protected by the basic patent*" was ambiguous.

8. The agent replied on 18 May 2020. She noted the examiner's analysis of the provisions of Article 2 and Article 1(b) as requiring that the product which was the subject of an SPC request should be a combination of active ingredients from a single medicinal product, but not a combination of active ingredients from multiple medicinal products. However, she reiterated that *binimetinib* and *encorafenib* had each received an MA as a mono-product, but significantly with each product being indicated for use in combination with the other. Moreover, she restated that both of these products had received an MA for the first time and that there was nothing in the SPC Regulation which expressly forbade an SPC for such a "loose" combination in such circumstances.

9. The agent contended that the simultaneous first-time approval of both active products, including labelling indicating they were to be taken in combination, was in contrast to previous CJEU decisions on combination SPCs based on other mono-product MAs with similar "take in combination" language on the label. In this regard she cited the UKIPO decision in the case SPC/GB04/037 (*Yeda*) where one element of a combination product had previously been approved and was not the subject of the MA on which the SPC had been based.

10. She reminded the examiner that one of the fundamental objectives of the SPC Regulation was to encourage *"all pharmaceutical research … without any discrimination*" (para. 29 - *Explanatory Memorandum on the SPC Regulation*). She argued that it was clearly the intention of the legislator to allow the grant of an SPC for all authorised combinations without discrimination between fixed-dose or *"*loose*"* combinations. Furthermore, she reported that the corresponding SPC application had already been granted by the Slovenian Patent Office, and the Norwegian Office had stated it was satisfied that the Article 3(b) requirements had been met.

11. Lastly, in addressing the examiner's objection to the proposed product identity, the

agent requested that the definition of the product be amended as follows: - *"Combination of binimetinib and encorafenib, each optionally in the form of a pharmaceutically acceptable salt or solvate thereof"*. She added that such an amendment clearly and unambiguously specified the active ingredients of the present combination of active ingredients and defined the forms of *binimetinib* and *encorafenib* covered by the basic patent.

12. On 23 June 2020 the agent emailed the examiner asking for a stay on the further prosecution of the case pending the outcome of an appeal before a court in Germany against a decision by the German office (the DPMA) to refuse the corresponding SPC application. This stay was duly granted by the examiner on 23 June 2020. On 2 November 2020 the agent wrote again to ask that the stay on prosecution be lifted.

13. The examiner responded on 6 November 2020 to the issues raised in the agent's letter of 18 May 2020. She reiterated her objection under Article 3(b) on the basis that, notwithstanding the MAs issued for the mono-products, there was no single authorisation to place the combination of the two active ingredients on the market as a medicinal product.

14. She explained that, while each product is clearly indicated for use with the other in both authorisations, the CJEU has ruled in the case C-673/18 (*Santen*) that the indication (i.e. the therapeutic application) was not relevant in the definition of the "product". She concluded by pointing out that, as an SPC had already been granted for each individual product and taking into account Article 4 *"Subject-matter of protection"* and Article 5 "*Effects of the certificate"* of the SPC Regulation, these SPCs guaranteed protection for each of the active ingredients - whether used individually or in combination.

15. Responding to the agent's reference to the *Explanatory Memorandum on the SPC Regulation* and specifically to the objective of the encouragement of all pharmaceutical research, the examiner cited paragraph 55 of the *Santen* judgement referred to earlier: -

> *55 Thus, as is apparent from paragraph 11 of the Explanatory Memorandum referred to in paragraph 45 above, the EU legislature intended, in establishing the SPC regime, to protect not all pharmaceutical research giving rise to the grant of a patent and the marketing of a new medicinal product, but to protect research leading to the first placing on the market of an active ingredient or a combination of active ingredients as a medicinal product (see, to that effect, judgment of 21 March 2019, Abraxis Bioscience, C-443/17, EU:C:2019:238, paragraph 37).*

The examiner concluded by maintaining her objection under Article 3(b) and stating that she now proposed to reject the SPC request.

16. The agent replied by email on 12 November 2020 to request a hearing and this was arranged for 21 January 2021. Because of the ongoing Coronavirus pandemic and the IPOI office being closed to the public, it was agreed that the hearing would take place by videoconference.

17. On 14 December 2020 the agent filed a detailed pre-hearing submission accompanied by SPC grant certificates from Bulgaria, Cyprus, Hungary, Malta and Slovenia, plus an English translation of a first office action from Norway.

18. The agent stated that the applicant had initially intended to pursue an authorisation for a fixed combination, but that they were mandated by the EMA to seek two separate MAs for the mono-products, albeit with language in both of the SmPC documents that each was indicated in combination with the other. In other words, the agent explained that the applicant did not have the option to pursue an MA for a fixed dose combination of the two active ingredients.

19. The agent referred to the accompanying grant certificates from the five EU/EEA Member States that had already granted the SPC request and she reminded the examiner that another objective of the SPC Regulation was to provide a uniform solution within the EU/EEA. The agent also reported that the appeals against pending refusals in Germany and other countries were no longer being pursued for commercial reasons.

20. The agent explained why the examiner should take a more general or "teleological" perspective on the SPC Regulation regarding fixed and so-called "loose" combination products. In this respect she did not accept the examiner's view that the citation of paragraph 55 from the CJEU in the *Santen* case was relevant and she referred to the Recitals attached to the SPC Regulation.

21. The agent went into much detail to discuss and analyse the interpretation of Article 1(b), Article 2 and Article 3 of the SPC Regulation. In particular, she referred to the CJEU rulings in C-322/10 (*Medeva*) and C-433/10 (*Georgetown*) to argue that the guidance provided by the court for fixed combinations exemplified a "purposive" interpretation of the SPC Regulation which could equally be applied to "loose" combinations. She summarised these decisions as indicating that *"… an SPC for A can be based on a marketing authorisation for*

A+B." Taking this argument one step further she argued that the principle established in *Medeva* could be, as a corollary, "*equally applicable to the reverse case*" - namely where an SPC is sought for a combination of A+B (as identified in the claims of the basic patent) and where the approved medicinal product, whilst only containing one of the claimed active ingredients A, is in accordance with the SmPC to be used in conjunction with the other specific active ingredient B.

22. The agent went on to argue against the examiner's interpretation of Article 3(b) and the CJEU ruling in the *Santen* case – namely that "*In other words, there is no single authorisation to place this combination of active ingredients on the market as a medicinal product*." She suggested that the facts of *Santen* were different to the present case as it concerned an attempt by the applicant to obtain an SPC based on a second medical use patent where the active ingredient had been the subject of a previous marketing authorisation for a different use. She noted that in the present case there has been no earlier MA for either *binimetinib* or *encorafenib* so that the decision by the court was not relevant.

23. Shortly before the hearing on 12 January 2021 the agent provided supplementary information specifically related to the product development pathway of the two medicinal products and the EMA regulatory approval pathway itself.

24. At the hearing on 21 January 2021 the applicant was represented by Anna Hally (of Hanna Moore + Curley) and Garreth Duncan (of D Young & Co.) On the side of the IPOI , in addition to myself and Dolores Cassidy (the examiner who handled the case), Fergal Brady (another SPC examiner) also participated.

ANALYSIS

25. The applicant is seeking an SPC for the product (as amended on 18 May 2020) "*Combination of binimetinib and encorafenib, each optionally in the form of a pharmaceutically acceptable salt or solvate thereof*". In order to satisfy Article 3(b) of the SPC Regulation, the applicant has cited two marketing authorisations issued on the same date for the single active ingredients *binimetinib* and *encorafenib* respectively. In the SmPC annex for both products, under Section 4.1 - Therapeutic indications, each respective single active ingredient is indicated for use in combination with the other for the treatment of adult patients with certain types of cancer.

26. The applicant has argued that it is entitled to the grant of an SPC for the combination

of the two active ingredients on the basis of these two authorisations and because it was not possible for it to apply for a single authorisation for the combination product itself.

27. Article 3 prescribes the conditions for obtaining a certificate: -

> *A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:*
> *(a) …*
> *(b) a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC or Directive 2001/82/EC, as appropriate;*
> …

28. It is noteworthy that Article 3(b) is focussed on an authorisation for a product. Accordingly it should be read in conjunction with the definition of "*product*" in Article 1(b).

Article 1(b) provides: -

> *'For the purposes of this Regulation, the following definitions shall apply:*
> *(a) …;*
> *(b) "product" means the active ingredient or combination of active ingredients of a medicinal product;*

29. The question of interpretation of Article 1(b) arose in 2005 from a referral by the Patent Court in the UK to the CJEU in the case C-202/05 (*Yissum*). One of the questions put to the Court in paragraph 11 read: -

> *"In a case in which the basic patent protects a second medical application of a therapeutic agent what is meant by "product" in Article 1(b) of the Regulation [No 1768/92] and in particular does the application of the therapeutic agent play any part in the definition of "product" for the purpose of the Regulation?"*

30. The Court ruled: -

> *"Consequently, the answer to the question referred must be that Article 1(b) of Regulation No 1768/92 is to be interpreted as meaning that in a case where a basic patent protects a second medical use of an active ingredient, that use does not form*

an integral part of the definition of the product."

31. In reaching this conclusion, the Court, in paragraph 17, referred to its decision in an earlier case C-431/04 (*MIT*), to emphasise that "… the concept of '*product'* referred to in Article 1(b) of Regulation No. 1768/92 must be interpreted strictly to mean '*active substance*' or '*active ingredient'*.

32. Indeed, in paragraph 18 the Court was even more explicit –

"It follows that the concept of 'product' cannot include the therapeutic use of an active ingredient protected by a basic patent."

33. In paragraph 19 the Court also referred to its decision in the case C-31/03 (*Pharmacia Italia*), in which it held: -

"It follows, first, that the decisive factor for the grant of the certificate is not the intended use of the medicinal product … ."

34. During the examination of the current case, the examiner referred to a more recent ruling from the CJEU in case C-673/18 (*Santen*) confirming this approach in paragraph 46: -

"That strict view of the term 'product' was given concrete form in Article 1(b) of Regulation No 469/2009, which defines that term by reference to an active ingredient or combination of active ingredients and not by reference to the therapeutic application of an active ingredient protected by the basic patent or a combination of active ingredients protected by that patent."

35. Article 4 of the SPC Regulation provides for the "*Subject-matter of protection*" as follows: -

"Within the limits of the protection conferred by the basic patent, the protection conferred by a certificate shall extend only to the product covered by the authorization to place the corresponding medicinal product on the market and for any use of the product as a medicinal product that has been authorized before the expiry of the certificate."

In other words, the protection conferred by an SPC is to extend only to the product covered

by the authorisation for the corresponding medicinal product.

36. Furthermore, in paragraphs 118 – 123 of a ruling in November 2019 in the Irish High Court (Commercial Division) between *Merck Sharp & Dohme Corp*. and *Clonmel Healthcare Limited* [2018 No. 3485P.], the judge, albeit in coming to a decision on a question under Article 3(d) of the SPC Regulation, gave a very detailed and thorough analysis of the interpretation of Article 3(b) along the lines I have outlined above.

38. The applicant has argued its initial intention was to pursue an application for a fixed combination but had concluded that this was never a feasible option because of the need to be able to reduce the dosage of either active ingredient due to possible treatment-related toxicity issues. The only option remaining was to seek approval for each product separately, albeit with "use in combination" language indicating this so-called "loose combination in Section 4.1 of the SmPC.

39. In the supplementary information submitted prior to the hearing, the applicant provided details on the EMA regulatory pathway and enclosed a copy of a publication from the Health and Food Safety DG of the EC entitled 'Volume 2A Procedures for marketing authorisation CHAPTER 1 MARKETING AUTHORISATION". Chapter 1, Section 5.5 relates specifically to fixed combinations as follows: -

> *"The combination of active substances within a single pharmaceutical form of administration according to this provision is a so-called 'fixed combination'.*
>
> *A key principle of the acquis is that there must be a marketing authorisation for each medicinal product that is put on the EU market. Therefore, the fixed combination definition is limited to active substances contained in a same pharmaceutical form of administration, the so-called 'fixed-combination'. The combination of active substances, where active substances are included in separate pharmaceutical forms and presented in a combination pack cannot be considered as fixed combination.*
>
> *In very exceptional circumstances, which must be considered on a case by case basis, the marketing of distinct medicinal products in the same package may be indispensable for public health reasons. Such reasons cannot be related to convenience or commercial purposes.*"

40. Such a "*same package*" form of two (or more) products is described as a "*combination pack*". The "*European Medicines Agency pre-authorization procedural advice for users of the centralised procedure*" document – an excerpt from which was also cited by the applicant - specifies that the applicant would be required to justify the marketing of such a combination on the basis of exceptional public health reasons. Effectively, the EMA appears to be differentiating between different types of these so-called "loose combinations". It appears that it is only in relatively rare circumstances that an authorisation would be granted for such a combination *per se*. The more common situation being as in the present case with the applicant being able to obtain separate authorisations for each medicinal product and including the "in combination with" language under the *Therapeutic Indications* section of the respective SmPC Annex

41. The official "Commission Implementation Decision" document issued by the EC for each of the medicinal products only names a single medicinal product – "*Mektovi – binimetinib*" or "*Braftovi - encorafenib*" in each case, both in the title itself and under Article 1. There is also a direction that the listed medicinal product be registered in the Community register of medicinal products - there is no mention of any combination in the text of either document.

42. It is only in Annex I – *Summary of Product Characteristics* (see Section 4 – *Clinical Particulars*) under *Therapeutic Indications* and in subsequent parts of each Annex I document that the use of a combination of the *binimetinib* and *encorafenib* for the treatment of patients is addressed e.g. therapeutic indications, posology and methods of administration, contraindications, etc.

43. The applicant has also referred to one of the fundamental objectives of the SPC Regulation as being the encouragement all pharmaceutical research without any discrimination. It should be noted that, as pointed out by the examiner, the applicant has already obtained "rewards" in the form of two SPC certificates, covering each of the separate medicinal products as mentioned in paragraph above.

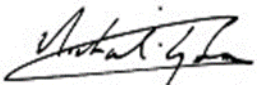
44. In light of the foregoing analysis I have concluded that it is not possible for the two individual marketing authorisations for *binimetinib* and *encorafenib* to be used in combination to satisfy the requirement in Article 3(b) of the SPC Regulation.

45. Therefore, the request for the grant of an SPC for the product *"the combination of the active ingredients binimetinib in combination with encorafenib, each optionally in the form of a pharmaceutically acceptable salt or solvate"* must be rejected because a valid authorisation to

place the product on the market under the provision of Article 3 (b) of the SPC Regulation has not been submitted.

DECISION

The request for the grant of Supplementary Protection Certificate No. 2019/010 by Array BioPharma AG for the product *"the combination of the active ingredients binimetinib in combination with encorafenib, each optionally in the form of a pharmaceutically acceptable salt or solvate"* is rejected under Article 10(2) of the SPC Regulation.



Dr. Michael Lydon
Hearing Officer
12 March 2021