Grounds of Decision in Respect of a Request by Georgetown University for the Grant of a Supplementary Protection Certificate (SPC) No. 2017/035

INTRODUCTION

1. This decision concerns a request for the grant of SPC no. 2017/035 filed on 15 August 2017 on behalf of Georgetown University by Anne Ryan & Co. related to the medicinal product "*Imlygic - talimogene laherparepvec*".

2. The legislation governing the granting of SPC applications in Ireland 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. In the application, the product (*'the active ingredient or combination of active ingredients of a medicinal product'* as defined in Article 1 (b) of the *SPC Regulation*) for which a certificate was requested was *talimogene laherparepvec*.

4. Patent no. EP 1 776 957 *('Use of herpes vectors for tumour therapy'*) was cited as the "basic patent" in support of the request, as required by Article 1(c) of the *SPC Regulation*.

5. Copies of marketing authorisations (MAs) EU/1/115/1064/001 & EU/1/115/1064/002 issued by the European Commission on 16 December 2015 were also submitted.

6. In her accompanying letter, the agent also mentioned the existence of other earlier SPC requests for the same product: - "*SPC application Nos 2016/027 and 2016/028 are also for talimogene laherparepvec and are based on EP 1 252 322 B2 and EP 1 252 323 B1, respectively. Both of these SPC applications are in the name of BioVex Limited, which was acquired by Amgen Inc. in 2011. We would ask you to note that Amgen Inc. is the exclusive licensee of Georgetown University in respect of the Basic Patent and any SPC granted thereon in the present case."*

7. The examiner issued a communication on 4 October 2018 to explain that the information provided under item 7(ii) of the SPC request was not sufficient for her to determine if the product was protected by the basic patent as required by Article 3(a) of the *SPC*

Regulation. In particular, it was not clear to her how claims 1 and 3 of the basic patent related *"implicitly, but necessarily and specifically"* to *talimogene laherparepvec*, or how a person skilled in the art would have been able to identify this product specifically in the light of all the information disclosed by the patent on the basis of the prior art at the priority date.

8. In support she cited a passage from Section 2.2.2 on page 15 of the EMA EPAR report on *talimogene laherparepvec* (EMA/734400/2015) detailing the nature of the modifications and the corresponding phenotypic changes generated by the modification of the particular herpes simplex virus (HSV) used to produce the desired therapeutic effects: -

> • *Functional deletion of the ICP34.5 gene enabling suppression of virus replication in normal tissue.*
> • *Deletion of the ICP47 gene enabling up-regulation of the US11 gene, resulting in increased replication of ICP34.5 deleted HSV, without reducing tumour selectivity.*
> • *Deletion of ICP47 gene ensuring display of cytoplasmic antigens on MHC Class I molecules enabling immunosurveillance by CD8+ T-cells.*
> • *Insertion of the human granulocyte macrophage colony-stimulating factor (hGM-CSF) expression cassette into the ICP34.5 loci, causing production and release of biologically active hGM-CSF stimulating a systemic cytotoxic immune response against tumour cells at distal locations.*

9. The examiner then referred to a question put to the CJEU in *Case C 121/17 (Teva)* – namely, *'What are the criteria for deciding whether "the product is protected by a basic patent in force" in Article 3(a) of Regulation No 469/2009?'* From the answer given by the Court in paragraph 52, she concluded that it appeared from publicly available information that the product *talimogene laherparepvec* had been created by a company, Biovex, Inc., which had not been founded until after the earliest priority date of the basic patent. She queried how a *"person skilled in the art"* would have been able to identify this product on the earliest priority date of the basic patent, namely 12 August 1997.

10. The agent replied on 4 March 2019 in support of her argument that the product was protected by the basic patent and referred the examiner to a document *"Protection of the Product by claims 1 + 3 of EP 1 776 957 B1"* which had been annexed to the original SPC request.

11. The agent regarded the examiner's objections based on Section 2.2.2 of the EPAR

document for *Imylgic* as being related to a "*structural description*" of the product and compared this with a passage from the CJEU ruling in the case *C-493/12 (Eli Lilly),* namely: - "*it is not necessary for the active ingredient to be identified in the claims of the patent by a structural formula."* She reminded the examiner that Article 69 EPC and Article 1 of the Protocol on Interpretation of Article 69 applied to the determination of the extent of protection afforded by the claims of the basic patent and claimed this had been reaffirmed by the CJEU in the *Teva* case*.* She also expressed the view that the judgment in that particular case was directed exclusively to combination products, and it should not be applied to a sole-component product as in the present case.

12. Finally, in the event that the examiner was not willing to grant the SPC request in the light of her arguments, the agent requested that further examination be stayed pending the outcome of two significant referrals before the CJEU – both cases concerning a product containing a single active ingredient. She cited these cases as C-114/18 (*Sandoz*) and C-650/17 (*Royalty Pharma*).

13. The examiner finally replied on 2 November 2020 to report that the request for a ruling in the *Sandoz* case had been withdrawn but more importantly the CJEU had issued its judgment in the *Royalty Pharma* case on 30 April 2020.

14. The examiner also provided a brief review of case law from the CJEU on the interpretation of Article 3(a) by way of the cases C-322/10 (*Medeva*), C-493/12(*Eli Lilly*) and *Teva*. She went on to refer specifically to paragraphs 47 and 48 of the Advocate General's Opinion in the *Royalty Pharma* case to conclude that the so-called 'two step test' in *Teva* could also be applied to medicinal products containing a single active ingredient.

15. As to the first aspect of the judgment in the *Royalty Pharma* case, the examiner stated her view that the product *talimogene laherparepvec* would not be specifically identifiable in the light of the disclosure in the basic patent by a person skilled in the art and based on that person's general knowledge in the relevant field at the filing date or priority date of the basic patent and on the prior art at that date.

16. She then looked at the second aspect of the *Royalty Pharma* case and quoted an abstract from the publication *Immunotherapy.* This document referred to a Robert Coffin as the inventor of *talimogene laherparepvec* and stated that his company BioVex Inc. had only been created in 1999. She argued that the product could therefore only have been developed

after 12 August 1998, i.e. after the application date of the basic patent in the present case. She concluded it was unlikely that *talimogene laherparepvec* would have been specifically identifiable by a skilled person at that date. She also stated this information also suggested that this product may have been developed following an independent inventive step.

17. The agent replied on 1 February 2021 with a 20-page submission which I shall not attempt to summarise here other than to report her conclusions that the product: - (A) satisfied both steps of the first test in *Royalty Pharma* for the reasons that; (1) it fell within the scope of the invention protected by the basic patent; and (2) it was '*specifically identifiable'* in the light of all the information disclosed by that patent, by a person skilled in the art, based on that person's general knowledge in the relevant field at the filing date or priority date of the basic patent and the prior art on that date; and (B) it satisfied the second test of the CJEU judgment in *Royalty Pharma.*

18. A hearing was requested, and this took place in a virtual teleconference format on 12 March 2021. The applicant was represented by Anne Ryan (of Anne Ryan & Co.). On the side of the office, in addition to myself as hearing officer and Dolores Cassidy (the examiner who handled the case), Fergal Brady (another SPC examiner) also participated. Prior to the hearing the agent submitted another written submission which was used by her as the basis to present the applicant's case at the hearing.

THE BASIC PATENT

19. The basic patent EP 1 776 957 is entitled '*Use of herpes vectors for tumour therapy*' and the description states in paragraph [0005] that an object of the invention is *'to provide a method of eliciting a systemic antitumor immune response in a patient who presents with multiple metastatic tumours without manipulating the patient's autologous tumour cells or identifying or purifying specific antigens'* and in paragraph [0006] *'to provide vectors for effecting this method.'*

20. More specifically in paragraph [0008] it is stated that the invention relates '*to a composition comprising a herpes simplex virus (HSV) that replicates in dividing cells and exhibits attenuated replication in non-dividing cells, and that comprises one or more nucleotide sequences encoding GM-CSF, wherein the GM-CSF is expressed, and a pharmaceutically acceptable vehicle for the virus for use in a method for treating a metastasis of melanoma*

cells by eliciting a systemic antitumor immune response in a patient who presents with multiple metastatic melanoma cells, wherein melanoma cells of the patient are inoculated with the composition, and wherein said composition induces an immune response that is specific for the melanoma cells and that kills cells of the inoculated melanoma cells and of a non-inoculated melanoma cells.'

21. An example of a mutated virus useful in the methods of the invention is given in paragraph [0010] as a herpes simplex virus e.g., a HSV type-1 (HSV1) virus that is incapable of expressing both (i) a functional ICP34.5 gene product and (ii) a ribonucleotide reductase.

ANALYSIS

22. There has been considerable written communication between the examiner and the agent in this case focussed on the interpretation of Article 3(a) of the *SPC Regulation* and particularly in relation to the most recent CJEU judgments on this article in the *Teva* and *Royalty Pharma* cases.

23. The decision of the examiner to apply the test set out by the CJEU in *Teva* for Article 3(a) in the case of a single active ingredient product has been queried on several occasions by the agent. However, having looked at the case law, it does seem very clear to me from paragraph 49 of the AG's Opinion in the *Royalty Pharma* case that this test is equally applicable in all cases irrespective of whether a medicinal product is composed of a single active ingredient or a combination of several such ingredients.

> *49. In this context any distinction between a product consisting of a single active ingredient and a combination of active ingredients is not material for the purposes of this test and any suggested distinction between the two types of products would not be a meaningful one. What matters instead is that, as the Court said at paragraph 57 and the operative part of the judgment of 25 July 2018, Teva UK and Others (C-121/17, EU:C:2018:585), 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.*

24. Indeed, recently this issue was specifically referred to and endorsed in paragraph 78

of the Irish Court of Appeal's judgment in the case *Merck Sharp & Dohme Corp v Clonmel Healthcare Limited [2021] IECA 54.*

> *78. This suggests that the Advocate General was of the view that the test in Teva applies whether or not one, or more, active ingredient(s) is, or are, expressly mentioned in the claims of the basic patent, contrary to MSD's contention.*

25. It is on this basis I shall apply the test set out in *Teva* to the present case.

26. This SPC request is for the product *talimogene laherparepvec* and *Article 4 (Subject matter of protection)* of the *SPC Regulation* provides: -

> *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 authorisation to place the corresponding medicinal product on the market and for any use of the product as a medicinal product that has been authorised before the expiry of the certificate.*

27. In this case the '*product covered by the authorisation to place the corresponding medicinal product on the market'* is described on page 15 of the of the EMA EPAR document for *talimogene laherparepvec* under '*Section 2.2.2. Active Substance'*. As I mentioned in paragraph 8 the examiner cited this description in her first communication to the agent. I repeat them here: -

> *'Talimogene laherparepvec was generated by modifying the wild type HSV-1 genome (new isolate JS1) in two regions. The nature of the modifications and the resulting phenotypic changes that bring about the desired therapeutic effects of talimogene laherparepvec are as follows:*
>
> - *functional deletion of the ICP34.5 gene enabling suppression of virus replication in normal tissue;*
> - *deletion of the ICP47 gene enabling up-regulation of the US11 gene, resulting in increased replication of ICP34.5 deleted HSV, without reducing tumour selectivity;*
> - *deletion of ICP47 gene ensuring display of cytoplasmic antigens on MHC Class I*

molecules enabling immunosurveillance by CD8+ T-cells, and

- *insertion of the human granulocyte macrophage colony-stimulating factor (hGM-CSF) expression cassette into the ICP34.5 loci, causing production and release of biologically active hGM-CSF stimulating a systemic cytotoxic immune response against tumour cells at distal locations.'*

28. As mentioned in my summary of the basic patent at paragraphs 19-21, the specific composition of the invention is derived from a suitably mutated virus such as the particular herpes simplex virus strain, HSV-1, which has been genetically modified by: -

(1) deletion of the ICP34.5 gene, and

(2) insertion in the disabled virus genome of one or more nucleotide sequences encoding a particular immunomodulatory protein, GM-CSF, which is known to stimulate a patient's immune system to recognise and destroy melanoma cells.

29. In comparing the functional features of the product described in the basic patent to those of *talimogene laherparepvec* in the EPAR document, I note that the latter was generated by modifying the particular HSV-1 genome in <u>two</u> regions, namely in the ICP34.5 <u>and</u> the ICP47 genes. However, the product described in the basic patent <u>only</u> mentions and claims the deletion of the ICP34.5 gene and is completely silent in relation to the ICP47 gene or to any potential beneficial therapeutic effects resulting from its deletion. Given that ICP47 is understood to function so as to block antigen presentation in infected cells, its disablement in the genome would result in the virus not conferring on infected tumour cells properties that would protect such cells from the host's immune system. This suggests to me that the therapeutic effects of the product of the basic patent would be of a lesser magnitude and efficacy that than of the product defined in the EPAR document.

30. The agent has argued at some length that claims 1 and 3 of the basic patent are fully supported in Annex 1 of the EPAR document specifically at items 2.1, 3, 4, 5.1, 5.2 and 6. However, her analysis omits to account for, or to explain, the absence of any mention whatsoever of the ICP47 gene in the patent. Her arguments seek to map the claims of the basic patent onto the features of the product as defined in the EPAR document. It seems to me one must first look at the definition of the product which is the subject of the MA and then seek to determine whether this forms part of the invention within the basic patent in its totality,

rather than focussing on the claims.

31. For the first step of the test according to the CJEU, it is necessary to consider the matter from the perspective of the *'person skilled in the art'* and to ask whether such a person can understand, without any doubt, on the basis of their general knowledge, and in the light of the description and drawings of the invention, whether the active ingredient *'must necessarily, in the light of the description and drawings of that patent, fall under the invention covered by that patent'.*

32. In this regard I have also noted a comment by the judge in paragraph 69(a) of the earlier High Court (Commercial) case of *Merck Sharp & Dohme Corp v Clonmel Healthcare Limited [2018 No. 3485 P.]* which also sheds light as to the role of the invention versus that of the claims within the basic patent:-

> *' …Similar language emphasising the importance of the invention is used elsewhere in the judgment. In my view, as I previously noted in my judgment in Gilead v. Teva, 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.'*

33. Therefore, I believe that the active ingredient *talimogene laherparepvec*, as described in the EPAR document, is not the same active ingredient as described and claimed in the basic patent. In other words, *talimogene laherparepvec* does not *'fall under the invention covered by that patent'* and so I conclude that the product of the SPC request fails the first step of the *Teva* test.

34. The second part of the *Teva* test sets out 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 the 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'*.

35. In her pre-hearing submission the agent argued that what this meant was *'not that the product must be identified by the skilled person at the priority date or the filing date of the basic patent, but rather that the skilled person must be able to identify it, i.e. the skilled person must have access to means capable of identifying the active ingredient, which is* ***specifically***

identifiable *by reference to the functions specified in the claims of the basic patent.'*

36. On this basis she argued that *'a skilled person working in the field of cancer therapy and being provided with the basic Patent and the product of the Marketing Authorisation, would immediately recognise how specifically the claims of the basic Patent identify the technical details of the authorised product, in particular the specific herpes simplex virus type, the insertion and expression of the GM-CSF gene and the functional abolition of the ICP34.5 gene. Therefore, if the skilled person would be provided with the (product of the) Marketing Authorisation as well as the basic Patent, he would consider that the basic Patent necessarily and specifically relates to the product and that the product is specifically identifiable, in light of all the information disclosed in the Patent, based on his general knowledge in the field at the filing date or priority date of the basic Patent and on the prior art at that date. … .'*

37. I believe this argument fails on the basis that there is no pointer, hint or suggestion as to the role of the ICP47 gene and the benefit arising from its inactivation/deletion in the basic patent.

38. As mentioned in paragraph 9, the examiner had referred to publicly available information to argue that *talimogene laherparepvec* had been created by a company which had not been founded until after the earliest priority date of the basic patent. Accordingly, she had queried how a *"person skilled in the art"* would have been able to identify the product on the earliest priority date of the basic patent, namely 12 August 1997.

39. Indeed, as also referred to previously in paragraph 6, the agent, in her letter accompanying the application request, herself referred to the existence of two earlier SPC requests for the same product: - "SPC application Nos 2016/027 and 2016/028 are also for *talimogene laherparepvec* and are based on patents EP 1 252 322 B2 and EP 1 252 323 B1, respectively."

40. I have briefly examined both patents and noted that they share the same priority dates of 21 January 2000 i.e. almost 2½ years after the earliest priority date of the basic patent in suit. Both patents refer explicitly to the inactivation/deletion of the ICP47 gene, and this feature is included in the claims of both. Indeed, this office granted SPC No. 2016/027 for *talimogene laherparepvec* and SPC No. 2016/028 was subsequently withdrawn as it related to the same product.

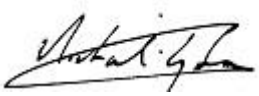
41. All the available evidence and analysis indicates to me that the product *talimogene*

laherparepvec could not have been *'specifically identifiable by a person skilled in the art at the priority date of the basic patent in the light of all the information disclosed by that patent'* and so it fails the second step of the *Teva* test.

42. Therefore, I have concluded that this SPC request does not comply with Article 3(a) of *SPC Regulation (EC) 469/2009* because the basic patent in force, EP 1 776 957, does not protect the product *"Imylgic - talimogene laherparepvec"*.

DECISION

The request for the grant of Supplementary Protection Certificate No. 2017/035 by Georgetown University for the product *"Imlygic - talimogene laherparepvec"* is rejected under Article 10(2) of the SPC Regulation.



Dr. Michael Lydon
Hearing Officer
19 May 2021