Intellectual Property Office

BL O/1016/24

24 October 2024

COUNCIL REGULATION (EC) 469/2009
CONCERNING THE CREATION OF A
SUPPLEMENTARY PROTECTION CERTIFICATE
FOR MEDICINAL PRODUCTS

APPLICANT	Genmab A/S
ISSUE	Whether SPC applications SPC/GB19/057, SPC/GB19/059, SPC/GB19/060, SPC/GB20/035, SPC/GB21/070 and SPC/GB21/071 meet the requirements of Article 3(b) of the Regulation
HEARING OFFICER	Dr Rowena Dinham

DECISION

1 This decision relates to six applications for supplementary protection certificates (SPCs) in the name of Genmab A/S. The details of these six SPC applications including the product definitions are summarised in Table 1 below.

Table 1

SPC Number	Product	First MA in the UK (or part thereof)	MA Grant Date
SPC/GB19/057	Daratumumab, lenalidomide & dexamethasone	EU/1/16/1101/001-002	28/04/17
SPC/GB19/059	Daratumumab, bortezomib, melphalan & prednisolone	EU/1/16/1101/001-002	18/12/18
SPC/GB19/060	Daratumumab, bortezomib & dexamethasone	EU/1/16/1101/001-002	28/04/17

SPC/GB20/035	Daratumumab, bortezomib, thalidomide & dexamethasone	EU/1/16/1101	20/01/20
SPC/GB21/070	Daratumumab, cyclophosphamide, bortezomib & dexamethasone	EU/1/16/1101	21/06/21
SPC/GB21/071	Daratumumab, pomalidomide & dexamethasone	EU/1/16/1101	21/06/21

2 The above SPC applications rely on basic patent EP(UK) 2081595 B1, entitled "Anti-CD38 plus corticosteroids plus a non-corticosteroid chemotherapeutic for treating tumors", which was filed on 26 September 2007, with an earliest priority date of 26 September 2006, and was granted on 10 April 2019.

3 The marketing authorisation (MA) for the medicinal product "DARZALEX[1]" for the product daratumumab was granted following Commission Implementing Decision EU/1/16/1101 on 20 May 2016[2]. The date of the MAs quoted in Table 1 in respect of the combinations relate to the date that the centralised European marketing authorisation was varied, as a type II variation, to include the above combinations in the treatment of specific myeloma patients (SPC/GB19/057, SPC/GB19/059, SPC/GB19/060 and SPC/GB20/035) and for the treatment of newly diagnosed light chain amyloidosis (SPC/GB21/070 and SPC/GB21/071).

4 Throughout the examination process the Examiner has maintained their position that the above SPC applications do not satisfy Article 3(b) of Regulation (EC) 469/2009 ("the SPC Regulation")[3] because the MAs are not for the combination products indicated in Table 1 above. It is the Examiner's opinion that the varied authorisations only constitute an authorisation to place the product daratumumab on the market - the variations indicate how the various combinations of further active agents should be used in conjunction with daratumumab in certain therapeutic circumstances, and as such do not authorise the *combination products* for which a certificate is sought to be placed on the market.

5 It is the Applicant's view that a teleological interpretation of the SPC Regulation should be adopted to allow for so-called "loose combination" SPCs in situations

[1] DARZALEX is a Registered Trademark (RTM) in the UK

[2] SPC/GB17/077 for the product daratumumab, based on the basic patent EP(UK) 2567976 and MA EU/1/16/1101 of 20 May 2016, was granted on 1 September 2022. For clarity, as there is already a SPC for DARZALEX-daratumumab alone, then I note the applications would also fail under Article 3(d) if they were to fail under Article 3(b).

[3] 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; see CELEX Document 32009R0469; published in the Official Journal of the European Union L 152 16/6/2009. Whilst this is an EU instrument, it is now retained EU law and has not materially changed since Brexit.

where it is not possible to formulate the active ingredients of a combination in a single preparation, as in the present case. In essence the Applicant considers that an SPC for a "loose combination" of active ingredients is consistent with the purpose of the SPC Regulation because the effort required to obtain a MA for a "loose combination" product, in terms of time and money taken for clinical testing of the combination and its subsequent placement on the market, is no less demanding than that required for a combination of active ingredients that are formulated in a single preparation ("fixed combination"), or as a single active agent.

6 Following several rounds of correspondence, the matter came before me at a hearing on 15 August 2024, which took place by video conference. At the hearing, the Applicant was represented by Dr Daniel Selmi, of Three New Square, who was instructed by Dr Graham Lewis of J A Kemp LLP. Senior Examiner Dr Natalie Cole acted as assistant to the Hearing Officer.

7 During the hearing, Dr Selmi stated that, although there are six SPC applications at issue in the present case, the arguments arising on each overlap significantly. For procedural efficiency, Dr Selmi made his arguments by reference to SPC application SPC/GB20/035 (referred to as '035) understanding that, unless specifically stated to the contrary, the arguments also apply to applications SPC/GB19/057, SPC/GB19/059, SPC/GB19/060, SPC/GB21/070 and SPC/GB21/071. Specific reference to the other SPC applications at the hearing was made only when necessary. For clarity, I have followed the same approach in my decision below.

The Basic Patent – EP(UK) 2081595 B1

8 The basic patent concerns a combination therapy for the treatment of cancer comprising an antibody that binds to CD38, particularly daratumumab, a corticosteroid and a non-corticosteroid chemotherapeutic agent. There are two independent claims in the basic patent: claim 1 is a claim to the combination for use in the treatment of cancer in the "EPC2000 format" and claim 25 is a claim to the use of the combination in cancer treatment in the "Swiss-type" format.

9 Claim 1 of the basic patent reads as follows:

> *"A human IgG1 isotype antibody that binds CD38 for use in the treatment of cancer, wherein the antibody is for administration, or to be administered, in combination therapy with at least one corticosteroid, wherein said at least one corticosteroid comprises a glucocorticoid, and at least one non-corticosteroid chemotherapeutic agent, wherein said at least one non-corticosteroid chemotherapeutic agent comprises (i) thalidomide or a thalidomide analog and/or (ii) a proteasome inhibitor, and wherein said antibody comprises human light chain and human heavy variable regions, wherein the light chain variable region comprises a V_L CDR1 having the sequence as set forth in SEQ ID NO:13, a V_L CDR2 having the sequence as set forth in SEQ ID NO:14 and a V_L CDR3 having the sequence as set forth in SEQ ID NO: 15, and the heavy chain variable region comprises a V_H CDR1 having the sequence as set forth in SEQ ID NO:18, a V_H CDR2 having the sequence as set forth in SEQ ID NO:19 and a V_H CDR3 having the sequence as set forth in SEQ ID NO:20"*

10 The Examiner was satisfied that the basic patent claims protect each of the combinations indicated in Table 1 above.

Issues to be Decided

11 There is a single issue to be decided: do each of the SPC applications indicated in Table 1 above meet the requirements of Article 3(b) of the SPC Regulation?

The Relevant Law

12 Article 1 of the SPC Regulation defines various terms, of which Articles 1(a) and 1(b) are relevant to this decision and are reproduced below:

> *"For the purpose of this Regulation, the following definitions apply:*
>
> *(a) "medicinal product" means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;*
>
> *(b) "product" means the active ingredient or combination of active ingredients of a medicinal product;*
>
> *(c) …"*

13 Article 3 of the SPC Regulation concerns the conditions for obtaining an SPC; part (b) of this Article proposes that a certificate cannot be obtained if the product has not been the subject of a valid authorisation to place a medicinal product on the market (my emphasis):

> ***"3. 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…, as appropriate;*
>
> *(c) …*
>
> *(d) …"*

14 Article 4 of the SPC Regulation defines the subject matter of protection provided by the certificate:

> *"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 authorized before the expiry of the certificate."

15 Article 10 of the SPC Regulation sets out the conditions for grant or rejection of an SPC application as follows:

> ***Grant of the certificate or rejection of the application for a certificate***
>
> *1. Where the application for a certificate and the product to which it relates meet the conditions laid down in this Regulation, the authority referred to in Article 9(1) shall grant the certificate.*
>
> *2. The authority referred to in Article 9(1) shall, subject to paragraph 3, reject the application for a certificate if the application or the product to which it relates does not meet the conditions laid down in this Regulation.*
>
> *3. Where the application for a certificate does not meet the conditions laid down in Article 8, the authority referred to in Article 9(1) shall ask the Applicant to rectify the irregularity, or to settle the fee, within a stated time.*
>
> *4. If the irregularity is not rectified or the fee is not settled under paragraph 3 within the stated time, the authority shall reject the application.*
>
> *5. ……...*
> *6. ……...*

The Relevant Case law – Article 3(b)

16 In his skeleton arguments, and during the course of the hearing, Dr Selmi referenced a number of authorities he deemed relevant to the present case. I have summarised the relevant points of the authorities directly related to the requirements of Article 3(b) below and will refer to the remaining authorities during my analysis, as appropriate.

Case C-392/97 Farmitalia Carlo Erba Srl ("Farmitalia")[4]

17 *Farmitalia* obtained marketing authorisation for the medicinal products "ZAVEDOS[5] 5mg" and "ZAVEDOS 10mg", for the treatment of acute myelitic leukaemia in humans, the single active ingredient of which was idarubicin hydrochloride. The Deutsche Patentamt (German Patent office) issued a certificate for "the medicament ZAVEDOS containing as its active ingredient idarubicin hydrochloride", but refused to issue the certificate, which was primarily sought, for "idarubicin and salt thereof including idarubicin hydrochloride", which would cover various salts of idarubicin. The decision was appealed and was upheld by the Bundespatentgericht.

18 In its appeal brought before the Bundesgerichtschof, *Farmitalia* maintained its request for the grant of a certificate for "idarubicin and salts thereof including

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[4] For full text of the Farmitalia CJEU decision see ECLI identifier: ECL!:EU:C:1999:416; https://ipcuria.eu/case?reference=C-392/97

[5] ZAVEDOS is a RTM in the UK

idarubicin hydrochloride", and, in the alternative, for "idarubicin and idarubicin hydrochloride". The Bundesgerichtschof referred two questions to the Court of Justice of the European Union ("CJEU") the first being:

> *"Does Article 3(b) presuppose that the product in respect of which the grant of a protection certificate is sought is described as an "active constituent" in the authorisation for marketing as a medicinal product?*
>
> *Is, then, Article 3(b) not complied with where a single individual salt of an active ingredient is stated in the notice of authorisation to be an "active constituent", but the issue of a protection certificate is sought for the free base and/or for other salts of the active ingredient?"*

19 The CJEU summarised this question as (at paragraph [17]):

> *"By its first question, the national court asks, in substance, whether, on a proper construction of Article 3(b) of Regulation No 1768/92, the certificate can protect the product only in the specific form stated in the marketing authorisation."*[6]

20 The CJEU went on to answer this question as follows (at paragraph [22], my emphasis):

> *"Consequently, the answer to the first question must be that, on a proper construction of Regulation No 1768/92 and, in particular, Article 3(b) thereof,* ***where a product in the form referred to in the marketing authorisation is protected by a basic patent in force, the certificate is capable of covering that product, as a medicinal product, in any of the forms enjoying the protection of the basic patent.****"*

21 In reaching its finding the CJEU reasoned (at paragraphs [18] and [20]):

> *[18] "[…] while the certificate could protect only the particular salt form of the active ingredient mentioned as the active constituent in the marketing authorisation, whereas the basic patent protects the active ingredient as such as well as salts thereof, including the one which is the subject-matter of the marketing authorisation, any competitor would be able, after the basic patent had expired, to apply for and, in some circumstances, obtain marketing authorisation for a different salt of the same active ingredient, formerly protected by that patent. It would therefore be possible for medicinal products which were in principle, therapeutically equivalent to that protected by the certificate to compete with the latter. The result would be to frustrate the purpose of Regulation No 1768/92, which is to ensure the holder of the basic patent of exclusivity on the market during a given period extending beyond the period of validity of the basic patent."*
>
> *[20] "Moreover, it should be borne in mind that the 13th recital in the preamble to Regulation (EC) 1610/96 of the European Parliament and of the Council of 23 July 1996 which, by virtue of 17th recital, is also valid, mutatis mandis, for*

[6] Regulation No 1768/92 preceded Regulation (EC) No 469/2009

the interpretation inter alia of Article 3 of Regulation No 1768/92, states that the certificate confers the same rights as those conferred by the basic patent, with the result that, where the basic patent covers an active substance and its various derivatives (salts and esters), the certificate confers the same protection."

Yeda Research and Development Co Ltd v Comptroller General of Patents [2010] EWHC 1733 (Pat) ("Yeda")[7]

22 *Yeda* related to an appeal to the UK Patents High Court of a decision of the Hearing Officer of the Intellectual Property Office, concerning two SPC applications. The first application (referred to as "037") specified the product to be protected as "cetuximab in combination with irinotecan". The Hearing Officer had refused this application on the grounds that the MA on which the application was based was an authorisation for cetuximab alone and as such the application did not comply with Article 3(b)[8]. The second application (referred to as "038") specified the product to be protected as "cetuximab". The Hearing Officer had refused this application on the grounds that cetuximab was not protected by the basic patent and as such did not comply with Article 3(a). For the purposes of the present case, the relevant aspects of the judgment are those made in relation to application "037".

23 The MA, submitted in support of both "037" and "038", was for the medicinal product "ERBITUX[9]", the active ingredient of which was cetuximab, for treating certain cancers. The Summary of Product Characteristics ("SmPC") included a discussion of how ERBITUX was to be used in combination with another active ingredient, irinotecan, for the treatment of certain types of cancer. The Applicant argued that the MA submitted was sufficient basis to provide support for an SPC for the combination of cetuximab with irinotecan.

24 The Hearing Officer held (at paragraph [40]):

"[…] I have to concern myself with determining what exactly is the medicinal product that has been approved and not just with its use or uses. Furthermore, such a focus on what the product is, rather than what it does, is consistent with the fact that what it does can change in the life of the MA but the product itself does not. […]"

25 This was upheld by Lewison J (at paragraph [26]):

"[…] But as the case law shows, how a medicinal product is used does not form part of the identification of the product itself. In my judgment the brief references to irinotecan in explaining how cetuximab is used are wholly insufficient to amount to a marketing authorisation of a product consisting of both cetuximab and irinotecan. In short, I agree with the hearing officer for the reasons that he gave."

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[7] Yeda Research and Development Co Ltd v Comptroller General of Patents [2010] (EWHC) 1733 (Pat); For full text see https://www.bailii.org/ew/cases/EWHC/Patents/2010/1733.html

[8] IPO decision BL O/066/10 Imclone Systems Inc. Ltd & Aventis Holdings Inc; For full text see https://www.ipo.gov.uk/p-challenge-decision-results/o06610.pdf

[9] ERBITUX is a RTM in the UK

26 The Court made clear that how a medicinal product is used does not form part of the identification of the product itself. The Court confirmed the Hearing Officer's view that the MA for ERBITUX, was for the single active ingredient cetuximab, and that although there were references in the MA to *the use* of another active ingredient, irinotecan, with cetuximab, the Court found that these references were *"wholly insufficient to amount to a marketing authorisation for a product consisting of both cetuximab and irinotecan"*. In this case, cetuximab and irinotecan were administered separately. Consequently, the appeal regarding "037" was dismissed.

Case C-322/10 Medeva ("Medeva")[10]; Case C-422/10 Georgetown ("Georgetown")[11]

27 In relation to Article 3(b) the CJEU in both *Medeva* and *Georgetown* was asked to consider the following question (see question 6 from *Medeva* and question 1 from *Georgetown*, as referred):

> *"Does… Regulation [No 469/2009] and, in particular, Article 3(b) permit the grant of a [SPC] for a single active ingredient or combination of active ingredients where:*
>
> *(a) a basic patent in force protects the single active ingredient or combination of active ingredients within the meaning of Article 3(a) of the SPC Regulation; and*
>
> *(b) a medicinal product containing the single active ingredient or combination of active ingredients together with one or more other active ingredients is the subject of a valid authorisation granted in accordance with Directive 2001/83/EC or 2001/82/EC which is the first MA that places the single active ingredient or combination of active ingredients on the market?"*

28 The CJEU summarised this question, referred from the UK Courts, as (at paragraph [29]):

> *"By its sixth question, the Court of Appeal asks, in essence, whether Article 3(b) of Regulation No 469/2009 may be interpreted as not precluding the competent industrial property office of a member state from granting a SPC for a combination of two active ingredients, corresponding to that specified wording of the claims of the basic patent relied on, where the medicinal product for which the MA is submitted in support of the SPC applications contains not only that combination of the two active ingredients but also other active ingredients."*

29 In *Medeva* the CJEU went on to answer this question as follows (my emphasis):

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[10] Medeva BV v Comptroller General of Patents, Designs and Trade Marks; Case C-322/10; For full text of the Medeva CJEU decision see ECLI identifier: ECL!:EU:C:2011:773; https://ipcuria.eu/case?reference=C-322/10

[11] Georgetown University and Others v Comptroller General of Patents, Designs and Trade Marks; Case C-422/10; For full text of the Medeva CJEU decision see ECLI identifier: ECL!:EU:C:2011:776; https://ipcuria.eu/case?reference=C-422/10

> *"Article 3(b) of Regulation No 469/2009 must be interpreted as meaning that, provided other requirements laid down in Article 3 are also met, that provision does not preclude the competent industrial property office of a Member state from granting a supplementary protection certificate for a combination of two active ingredients, corresponding to that specified in the wording of the claims of the basic patent relied on,* ***where the medicinal product for which the marketing authorisation is submitted in support of the application for a supplementary protection certificate contains not only that combination of the two active ingredients but also other active ingredients****."*

30 In the related *Georgetown* judgment, the CJEU answered this question as follows (my emphasis):

> *"Article 3(b) 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 meaning that, provided the other requirements laid down in Article 3 are also met,* ***that provision does not preclude the competent industrial property office of a Member State from granting a supplementary protection certificate for an active ingredient specified in the wording of the claims of the basic patent relied on, where the medicinal product for which the marketing authorisation is submitted in support of the supplementary protection certificate applications contains not only that active ingredient but also other active ingredients.****"*

31 In reaching its judgment in *Medeva* the CJEU gave its reasoning in paragraphs [30]-[41]. I have set out the most relevant of these paragraphs below (my emphasis):

> *[30] "First, it must be noted that the fundamental objective of Regulation No 469/2009 is to ensure sufficient protection to encourage pharmaceutical research, which plays a decisive role in the continuing improvement in public health"*
>
> *[33] "[…] at present medicinal products placed on the market, in particular for complex diseases, often consist of active ingredients for multiple therapeutic uses which can be administered to patients in a single preparation. Similarly, vaccines are often developed, in particular having regard to the recommendation of the health authorities of the Member states, in the form of multivalent vaccines."*
>
> *[34] "If the holder of such a basic patent relating to an innovative active ingredient or an innovative combination of active ingredients were to be refused a SPC on the ground that, in the commercial version of the medicinal product which places that active ingredient or combination on the market for the first time, the active ingredient or the combination coexists in the medicinal product alongside other active ingredients or combinations which have other therapeutic purposes and may or may not be protected by another basic patent in force, the fundamental objective of Regulation No 469/2009, which is to ensure sufficient protection to encourage pharmaceutical research and play a decisive role in the continuing improvement in public health could be undermined."*

[35] "First, the holder of such a patent would enjoy only the period of effective protection conferred by the patent, which, according to European Union legislature is insufficient to cover the investment put into pharmaceutical research, which is why that legislature created a SPC for medicinal products designed to make up for that insufficiency. Second, such an approach would tend to favour the development of monovalent medicinal products, in particular vaccines, which may not be in the interests of patients and national public health authorities. In such a situation, the holders of such patents would be forced to develop commercially and maintain on the market medicinal products containing only the active ingredients specified as such in the basic patent in order to obtain a MA for a medicinal product covering those active ingredients which, as such the holder could be certain would confer entitlement to a SPC."

[37] "The requirement in Regulation No 469/2009 that the "product" must be covered, as a medicinal product, by a MA confirms that approach in that that requirement does not itself rule out the possibility that the MA may cover other active ingredients contained in such a medicinal product. Moreover, in accordance with Article 4 of Regulation 469/2009, a SPC is intended to protect the "product" covered by the MA, not the medicinal product as such."

[38] "Furthermore, such a situation corresponds to that described in paragraphs 34 and 39 of the explanatory memorandum, in which the Commission of the European Communities stated, first, that the requirement that the product must have obtained a valid MA is met "if the proprietary medicinal product containing it has been granted the [MA] concerned" and, second, that in such a situation, "where the product authorised consists of a combination of compound X and another active ingredient, only compound X will be protected by the certificate"."

[39] "In accordance with Article 5 of Regulation No 469/2009, a SPC thus granted in connection with such a product confers, upon the expiry of the patent, the same rights as were conferred by the basic patent in relation to the product, within the limits of the protection conferred by the basic patent, as provided for in Article 4 of the regulation. Accordingly, if, during the period in which the patent was valid, the patent holder could oppose, on the basis of his patent, all use or certain uses of his product in the form of a medicinal product ***consisting of such a product or containing it****, the SPC granted in relation to that product would confer on the holder the same rights for all uses of the product, as a medicinal product, which were authorised before the expiry of the certificate."*

32 Similar points were also made by the CJEU in paragraphs [24]-[35] in *Georgetown*.

Case 631/13, Forsgren ("Forsgren")[12]

33 *Forsgren* concerned the use of Protein D from Haemophilus influenzae as a carrier protein in a vaccine for pneumococcus. In the latter, Protein D had no therapeutic effect, but was covalently bonded to other active ingredients.

34 The case was appealed to the Oberster Patent- und Markensenat where the Court referred three questions to the CJEU. Referred question 2(a) considered application of Article 3(b) and the definition of the therapeutic indications covered by the wording of the MA. The issue concerned the relevance of Protein D being an active ingredient in some scenarios, but not in the circumstances of the medicinal product at issue. At paragraph [39] the CJEU held:

> *"Article 3(b) of Regulation No. 469/2009 must be interpreted as precluding the grant of an SPC for an active ingredient whose effect does not fall within the therapeutic indications covered by the wording of the marketing authorisation."*

35 Referred question 2(b), concerned the relevance of the fact that Protein D enhanced the effect being expressly mentioned in the MA. At paragraph [54] the CJEU held:

> *"Article 1(b) of Regulation No 469/2009 must be interpreted as meaning that a carrier protein conjugated with a polysaccharide antigen by means of a covalent binding may be categorised as an "active ingredient" within the meaning of that provision only if it established that it produces a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indication of the marketing authorisation, a matter which it is for the referring court to determine, in light of all the facts of the dispute in the main proceedings."*

Decision O/711/22 Roche Glycart (23 August 2022) (Roche)[13]

36 *Roche* is a decision of the Intellectual Property Office, and although is not binding on me, the facts of the case and the arguments addressed in the decision are worth noting.

37 *Roche* concerned a combination of two active ingredients, obinutuzumab and bendamustine. The MA submitted in support of the application was a type II variation to a centralised European MA for the medicinal product "GAZYVARO[14]", the active ingredient of which was obinutuzumab. The SmPC included references of how GAZYVARO was to be used in combination with bendamustine for the treatment of patients with follicular lymphoma. The issue was whether the MA for GAZYVARO was a valid authorisation to place the combination of obinutuzumab and bendamustine on the market.

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[12] Arne Forsgren v Österreichisches Patentamt; Case 631/13; For full text of the Forsgren CJEU decision see ECLI identifier: ECL!:EU:C:2015:13; https://ipcuria.eu/case?reference=C-631/13
[13] IPO decision BL O/711/22, Roche Glycart AG relating to application SPC/GB17/055; For full text see https://www.ipo.gov.uk/p-challenge-decision-results/o71122.pdf
[14] GAZYVARO is a RTM in the UK

38 The Hearing Officer was not persuaded by the Applicant's submission that a teleological interpretation of the SPC Regulation should be adopted to allow for so-called "loose combination" SPCs. Having regard to the decision in *Yeda* the Hearing Officer held that there was only one active ingredient, obinutuzumab, in the medicinal product. Consequently, because the MA was to the single active ingredient, and not the combination, the Hearing Officer refused the SPC application on the grounds that it did not comply with the requirements of Article 3(b).

Newron Pharmaceuticals [2024] EWCA Civ 128 (Newron)[15]

39 The appeal in *Newron* centred on Article 3(b) of the SPC Regulation and the meaning of the term "product" in the context of a treatment for Parkinson's disease using the medicinal product "XADAGO[16]", the active ingredient of which was safinamide. XADAGO had been authorised for the treatment of Parkinson's disease as an add-on therapy to levodopa (L-dopa) given alone or in combination with other Parkinson's disease medications, known as Peripheral Decarboxylase Inhibitors (PDIs). The Applicant had sought an SPC for the combination of safinamide and levodopa/PDI, however the Hearing Officer of the Intellectual Property Office[17] held that the MA was for the single active ingredient safinamide not the combination.

40 The case ultimately came before the Court of Appeal where Birss LJ held (at paragraphs [32] and [35]):

> *[32] "[…] The question in the end under Art 3(b) is whether, assuming the product in question is safinamide in combination with levodopa and PDI, the marketing authorisation in the present case is an authorisation to place that on the market as medicinal product. […]"*

> *[35] "[…] The fact that there are further references to levodopa and (a few) to PDIs in the detailed parts, along with references to the clinical trials involving both, is not relevant to the fairly simple question what is the active ingredient in the medicinal product authorised by a given marketing authorisation. […]"*

41 He concluded at paragraph [36] (my emphasis):

> *"A point which emerged in argument before this court and which I believe puts the matter beyond doubt, is to* ***focus on what exactly it is that the holder [Newron] is authorised to do as a result of the marketing authorisation in question****. The answer here is that this marketing authorisation authorises Newron to market XADAGO (safinamide). That is all. There is no dispute that this marketing authorisation does not authorise Newron to put on the market any other active ingredient such as Levodopa (nor other PDIs). The evidence does not address whether Newron sells Levodopa, it does not matter.*

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[15] Newron Pharmaceuticals S.p.A v Comptroller General of Patents, Trademarks and Designs [2024] EWCA Civ 128; For full text see https://www.bailii.org/ew/cases/EWCA/Civ/2024/128.html; On appeal from Newron Pharmaceuticals S.p.A v Comptroller General of Patents, Trademarks and Designs [2024] EWHC 1471 (Ch)

[16] XADAGO is a RTM in the UK

[17] IPO decision BL O/1053/23 Newron Pharmaceuticals, SpA., relating to application SPC/GB15/046; For full text see https://www.ipo.gov.uk/p-challenge-decision-results/o105322.pdf

However, if Newron was putting Levodopa on the market at the moment there would need to be a further marketing authorisation for that."

42 The Court of Appeal reasoned that the correct approach, when determining what is the product of a given MA for the purposes of Article 3(b), is to focus on what the MA in question authorises the holder to do. Accordingly, although there were references to Levodopa and PDIs in the MA, the Court found that this did not enable *Newron* to market the product safinamide in combination with Levodopa and/or PDI and the appeal was dismissed.

Definitions

43 Before I begin looking at the arguments, it is helpful to consider the terms being used to refer to different types of combinations in the present case to ensure there is a consistent understanding.

44 During the hearing reference was made to "loose combinations" and "fixed combinations". I will use the term "loose combination" to identify the situation where what is being referred to is a combination of two or more active ingredients, each of which is administered separately and does not form part of a single pharmaceutical preparation, such as a tablet or solution. Thus, in a "loose combination" of two active ingredients, A and B, each can be administered either at the same time or with a delay between them. They can be administered in different pharmaceutical forms, e.g. A could be administered as an oral tablet and B could be administered as a solution for injection, and the amount of A and B administered relative to each other can be varied or changed depending on the patient and the condition being treated.

45 This is in contrast to "fixed combinations" where the active ingredients of the compositions are administered at the same time and in the same pharmaceutical form, that is A and B are formulated together in a single pharmaceutical preparation. These definitions of both "loose combinations" and "fixed combinations" are consistent with those used by Dr Selmi.

46 The product of SPC application '035 is a combination of daratumumab, bortezomib, thalidomide and dexamethasone and is an example of a loose combination. There is no overlap between the active ingredients of this combination, each is kept and is administered separately from each other, such that the dose of each active ingredient can be adjusted depending on the patient. Thus, it is important to note that the loose combination in the present case is not a combination in the physical sense.

Arguments and Analysis

47 The key issue I must decide is whether, in accordance with Article 3(b) of the SPC Regulation, the varied MA provided in support of SPC application '035 is a valid MA to place the product namely daratumumab, bortezomib, thalidomide, and dexamethasone, on the market as a medicinal product. In reaching my decision I must identify what is the active ingredient or active ingredients in the medicinal product covered by the MA for DARZALEX; is it a single active ingredient, as suggested by the Examiner, or is a combination of daratumumab, bortezomib, thalidomide, and dexamethasone, as suggested by the Applicant?

48 The MA in support of SPC application '035 is a type II variation to the MA for DARZALEX. As acknowledged in the skeleton arguments, Type II variations are provided in accordance with the Variations Regulation[18] and are defined as follows:

> *"Major variation of type II" means any variation which is not an extension and which is liable to have significant impact on the quality, safety and efficacy of the medicinal product concerned."*

49 Before implementation type II variations require prior approval, known as the "Prior authorisation" procedure, and annex II of the Variations Regulation set out variations which are classified as major variations of type II. The type II variation of the MA in the present case falls within the following classification:

> *"(a) variations related to the addition of a new therapeutic indication or to the modification of an existing one"*

50 The type II MA on which SPC application '035 relies was granted by the European Commission Decision C(2020)398 (final) of 20/01/2020 entitled:

> *"COMMISSION IMPLEMENTING DECISION of 20.1.2020 amending the marketing authorisation granted by Decision C(2017)2958(final) for "DARZALEX – daratumumab", an orphan medicinal product for human use"*

51 Section 2 of the SmPC, entitled "2. QUALITATIVE AND QUANTITATIVE COMPOSITION", states:

> *"Each 5 mL vial contains 100 mg of daratumumab (20 mg daratumumab per mL).*
> *"Each 20 mL vial contains 400 mg of daratumumab (20 mg daratumumab per mL).*
> *Daratumumab is a human monoclonal IgG1κ antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology."*

52 Section 4 of the SmPC entitled "4. CLINICAL PARTICULARS" contains a number of sections, of which section 4.1 "Therapeutic indications" reads as follows:

> *"DARZALEX is indicated…in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant."*

The Examiner set out their interpretation of the MA in their pre-hearing report dated 31 May 2024. Their position was that, in line with the Intellectual Property Office decision in *Roche* and the precedent in *Newron,* the present SPC application should not be granted because the Type II variation to the MA only constitutes an authorisation to place the product daratumumab on the market. The Examiner considered that the Type II variation indicates *how the combination of active ingredients should be used* in conjunction with daratumumab in certain therapeutic

[18] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products; see CELEX Document 02008R1234-20210513

circumstances and as such does not enable the combination of bortezomib, thalidomide and dexamethasone to be placed on the market.

53 Conversely, in his skeleton arguments and at the hearing, Dr Selmi argued that in *Roche* the Examiner and Hearing Officer applied an overly restrictive reading of the MA when identifying the medicinal product and product/active ingredients. He submitted that *MIT*[19], *GSK*[20], *Forsgren* and *Abraxis*[21] show that an active ingredient is a substance which has a therapeutic effect of its own which is covered by the therapeutic indications of the MA, and argued that *"it is immaterial whether the MA refers to the substance by the term 'active ingredient', what matters is that the substance in actual fact has that effect, as it does in this case"*. Dr Selmi emphasised this point by reference to section 4 of the SmPC, submitting that bortezomib, thalidomide and dexamethasone have a therapeutic effect on their own in respect of the therapeutic indication specified, arguing that *"it does not matter that those active ingredients only appear under the heading 'Therapeutic indications'. That is clear from the nature of the Variations Regulation…, and the fact that those other ingredients are clearly not aspects of how DARZALEX is used, as distinguishable from those cases that excluded the nature of the product by reference to their intended use (c.f. Pharmacia*[22]*, MIT, Yissum*[23] *and Santen*[24]*)"*.

54 He also went to lengths to explain the various combinations in each of the separate SPC applications, and uses of DARZALEX outlined in the Type II variation MA, with particular emphasis on the extensive studies that had taken place, and described at section 5 of the SmPC. These studies demonstrate the efficacy of the combination in the patient groups tested, and in Dr Selmi's opinion demonstrate that it is clear that bortezomib, thalidomide and dexamethasone (amongst the others) are indeed "*active ingredients in the sense required by the case law*" and as such this combination does constitute the medicinal product protected by the MA. He also argued that these studies are indicative of the effort required in obtaining the type II variation, and in his opinion point towards why protection in the form of an SPC should be granted for the combinations tested.

55 In Dr Selmi's opinion, to refuse an SPC based on a "loose combination" MA "*leads to unjustified discrimination between combinations of active ingredients that can be formulated in a single galenic preparation and 'loose combinations' – even though*

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[19] Massachusetts Institute of Technology; Case C-431/04; For full text of the MIT CJEU decision see ECLI identifier: ECL!:EU:C:2006:291; https://ipcuria.eu/case?reference=C-431/04

[20] GlaxoSmithKline Biologicals SA and Glaxosmithkline Biologicals, Niederlassung der Smithkline Beecham Pharma GmbH & Co. KG V Comptroller General of Patents, Designs and Trade Marks; Case C-210/13; For full text of the GSK CJEU decision see ECLI identifier: ECL!:EU:C:2013:762; https://ipcuria.eu/case?reference=C-210/13

[21] Abraxis Bioscience LLC v Comptroller General of Patents; Case C-443/17; For full text of the Abraxis CJEU decision see ECLI identifier: ECL!:EU:C:2019:238; https://ipcuria.eu/case?reference=C-443/17; https://ipcuria.eu/case?reference=C-31/03

[22] Pharmacia Italia SpA; Case C-31/03; For full text of the Pharmacia CJEU decision see ECLI identifier:ECLI:EU:C:2004:641

[23] Yissum Research & Development Company of the Hebrew University of Jerusalem v Comptroller General of Patents; Case C-202/05; For full text of the Yissum CJEU decision see ECLI identifier: ECL!:EU:C:2007:214; https://ipcuria.eu/case?reference=C-202/05

[24] Santen SAS v Directeur général de l'Institut national de la propriété industrielle;Case C-673/18; For full text of the Santen CJEU decision see ECLI identifier: ECL!:EU:C:2020:531; https://ipcuria.eu/case?reference=C-673/18

the active ingredients and therefore the 'product' may be the same" and submitted that the clinical studies required for loose combinations were no less demanding than comparable studies for fixed combinations. During the hearing Dr Selmi expanded on these points and the possible implications. He directed me to recital 3 of the SPC Regulation which states:

> *"Medicinal products, especially those that are the result of long costly research will not continue to be developed in the Community and in Europe unless they are covered by favourable rules that provide for sufficient protection to encourage such research."*

And recital 4 which explains:

> *"[…] the period that elapses between the filing of an application for a patent for a new medicinal product and authorisation to place the medicinal product on the market makes the period of effective protection under the patent insufficient to cover the investment put into the research."*

On this basis, Dr Selmi argued that by refusing SPCs for loose combinations many kinds of valuable pharmaceutical research will not get the protection they deserve. He set out the Applicant's view that in cases based on more complicated facts, and where there is a mismatch between the MA and SPC, as in *Farmitalia*, *Medeva*, and *Forsgren*, the CJEU has *"established an approach of construing the MA teleologically"*. Whilst each of these judgments do emphasise the importance of an outcome-driven approach to the interpretation of the SPC Regulation, the reasonings behind this differs in each case, and so I will consider Dr Selmi's arguments in relation to each of these CJEU decisions in turn in deciding whether there is any support for a broader interpretation of what constitutes the "product" of the MA and as required by Article 3(b) in relation to the facts of the present case.

56 Turning first to *Farmitalia*. Dr Selmi directed me to paragraph [18] of the judgment, where the CJEU accepted that a situation could arise where a certificate only protected the particular salt form of a given active ingredient defined in the MA, whereas the patent protects the active as well as alternative salts thereof, and after expiry of the patent a competitor could obtain a MA for an alternative salt of the same active ingredient. The result would be that medicinal products which were, in principle, therapeutically equivalent to that protected by the certificate could compete with the latter, and the CJEU found that this would frustrate the purpose of the SPC Regulation.

57 Whilst I acknowledge that the CJEU could be considered to have adopted an outcome driven approach to interpreting the SPC Regulation, I do not believe that this supports Dr Selmi's submission regarding the way in which the MA should be interpreted in the present case. In *Farmitalia* the CJEU considered the free active ingredient and salts or esters thereof to be therapeutically equivalent, taking into account the purpose of the SPC Regulation to provide sufficient protection to encourage pharmaceutical research. Furthermore, in referencing, at paragraph [20],

Regulation (EC) 1610/96[25] and particularly the 13th recital therein[26] the CJEU found that Article 3 of the SPC Regulation is to be interpreted as conferring the same rights as those conferred by the basic patent, with the result that, where the basic patent covers an active substance and its various derivatives (salts and esters), the certificate confers the same protection. Therefore, in *Farmitalia*, where the basic patent covered idarubicin and exemplified idarubicin hydrochloride, the medicinal product of the MA was idarubicin hydrochloride only, and the product of the SPC was "idarubicin and salts thereof including idarubicin hydrochloride", the CJEU reasoned that the **different forms of idarubicin are therapeutically equivalent**, and so the certificate should be capable of covering that product, as a medicinal product, in any of the forms enjoying the protection of the basic patent.

58 Dr Selmi's point here was that there was not a strict literal concordance between the medicinal product of the MA (idarubicin hydrochloride) and the certificate that the CJEU felt was warranted (i.e. idarubicin and salts thereof, including idarubicin hydrochloride, as disclosed in the basic patent), and that in grey areas Article 3(b) can be construed teleologically to allow the grant of the SPC under certain circumstances.

59 It is on this basis that, at the hearing, Dr Selmi argued that the MA for DARZALEX in the present case should be read as also including bortezomib, thalidomide and dexamethasone. He further argued that this is because we are in, what he referred to as, another grey area when dealing with 'loose combinations', and that refusal of such an SPC would be contrary to the intention of the SPC Regulation and inconsistent with the decision in *Farmitalia*. I do not agree with this assertion. It is clear to me that the CJEU in *Farmitalia* was focussing on medicinal products which were of a **different form** (such as derivatives, salts and esters) of the specific medicinal product of the MA, and were **therapeutically equivalent**, and indeed their reasoning focussed around frustrations to the purpose of the SPC Regulation arising where therapeutically equivalent medicinal products could compete with those protected by the certificate. In the present case the Applicant is not seeking a certificate for different forms of the specific medicinal product, nor are they seeking therapeutically equivalent medicinal products, and so I cannot draw parallels with the frustrations to the purpose of the SPC Regulation observed by the CJEU in *Farmitalia*.

60 Looking now at *Forsgren*, where similar to the situation in *Farmitalia,* the CJEU found appropriate once again to refer to the fundamental objective of the SPC Regulation which is to ensure sufficient protection to encourage pharmaceutical research. In this case, the carrier protein, Protein D, was considered to contribute to the induction of a specific immune response to the pneumococcal polysaccharides to which it is conjugated, beyond that of an adjuvant. The CJEU decided that in order for Protein D to be an "active ingredient" as required by the SPC Regulation it must produce "*a pharmacological, immunological, or metabolic action of its own which is covered by*

[25] Regulation (EC) No 1610/96 of the European Parliament and of the Council of 23 July 1996 concerning the creation of a supplementary protection certificate for plant protection products; see CELEX Document 31996R1610; published in the Official Journal of the European Union L 198 8/8/1996

[26] Recital 13 of Regulation (EC) 1610/96 reads: "*Whereas the certificate confers the same rights as those conferred by the basic patent; whereas, consequently, where the basic patent covers an active substance and its various derivatives (salts and esters), the certificate confers the same protection*".

the therapeutic indications of the marketing authorisation" in light of all the facts of the case in dispute. In this case, the Protein D was conjugated to various pneumococcal polysaccharides, and these conjugates (i.e. including Protein D) formed part of the medicinal product "SYNFLORIX[27]" .

61 Directing me specifically to paragraphs [51]-[54] of the judgment, Dr Selmi submitted that the pharmacological, immunological or metabolic action of the active ingredient is important when looking at the MA in the present case. In his opinion, *Forsgren* makes it clear that an active ingredient is something that produces a pharmacological, immunological, or metabolic action of its own which is covered by the therapeutic indications of the MA, and in the MAs for DARZALEX, each of the antibody, corticosteroid and non-corticosteroid components are having such an effect, and as such form part of the active ingredient and hence the product of the MA. He went on to clarify that in the present case it is the combination that is the new product, and that this interpretation is fully supported by the reasoning in *Forsgren*.

62 I accept that *Forsgren* is another example where the CJEU has taken a teleological approach to interpreting the SPC Regulation in light of the facts of that specific case. I also acknowledge that bortezomib, thalidomide and dexamethasone are active ingredients that have a pharmacological action of their own that are covered in the therapeutic indications of the MA. But again I find difficulty in finding that the CJEU's reasoning supports Dr Selmi's submission that bortezomib, thalidomide and dexamethasone are active ingredients **that form part of the product** of the MA for DARZALEX. In *Forsgren,* the medicinal product SYNFLORIX comprises the pneumococcal polysaccharides conjugated to their carrier proteins; both the pneumococcal polysaccharides and their carrier proteins form part of the approved medicinal product that is covered by the MA. Therefore, whilst I acknowledge that bortezomib, thalidomide and dexamethasone are active ingredients in the context of the therapeutic indications listed in section 4.1 of the SmPC, I do not see anything from *Forsgren* that would direct me to consider these as part of the approved medicinal product DARZALEX.

63 The final significant case that Dr Selmi relies upon for the endorsement of a teleological approach to the interpretation of the SPC Regulation is *Medeva* and *Georgetown*[28]. At the hearing Dr Selmi drew my attention to paragraphs [74], [78], [79] and [88] of the Advocate General's opinion (reproduced below):

> *[74] "It follows from my above observations that, as a general rule, on literal interpretation of Regulation No 469/2009 there can be no question of a supplementary protection certificate being granted for a multi-disease vaccine in which the combination of active ingredients is only partly patented. I shall now examine below first whether such a conclusion is compatible with the aims of Regulation No 469/2009. Since, in my view, the answer to that must be in the negative, I shall then complement that literal interpretation of Regulation No 469/2009 with a teleological interpretation."*

[27] SYNFLORIX is a RTM in the UK

[28]The sole question referred in Georgetown was the same as the sixth question referred in Medeva and therefore both cases were heard together. Whilst the CJEU issued separate final judgments, the answers to the respective questions were the same.

[78] "Against the background of that complex situation as regards interests, Regulation No 469/2009 sought to achieve a balanced solution taking due account of the interests of all parties. In view of the complexity of that balance of interests, it is necessary to proceed with great caution when making a teleological interpretation of the individual provisions of the regulation."

[79] "Nevertheless, it is in my view clear that the result of a literal interpretation of Regulation No 469/2009, according to which, in the case of medicinal products with multiple active ingredients only part of which is the subject-matter of a patent, no supplementary certificate can be granted, is not compatible with the objectives of Regulation No 469/2009"

[88] "The literal interpretation of Articles 1 to 3 of Regulation No 469/2009 must be complemented by a teleological interpretation which ensure that the rules on [SPCs] contained in those provisions can also be fully effective in respect of medicinal products in which the combination of active ingredients is only partly the subject-matter of the patent."

He argued that the Advocate General was emphasising the requirement for a teleological interpretation and not a literal interpretation of the SPC Regulation in order to be compatible with its aims and objectives, and in doing so made reference (at paragraph [88]) to *Farmitalia*, confirming that such an interpretation of the SPC Regulation was settled case law.

64 Dr Selmi went on to address the CJEU decision in *Medeva*, highlighting paragraphs [30], [31], [34], [35] and [36] (reproduced below) which endorsed the Advocate General's approach:

[30] "First, it must be noted that the fundamental objective of Regulation No 469/2009 is to ensure sufficient protection to encourage pharmaceutical research, which plays a decisive role in the continuing improvement in public health […]"

[31] "The reason given for the adoption of that regulation is the fact that the period of effective protection…is insufficient to cover the investment put into pharmaceutical research […]"

[34] "If the holder of such a basic patent relating to an innovative active ingredient or an innovative combination of active ingredients were to be refused a SPC on the ground that the commercial version of the medicinal product…the active ingredient or the combination coexists in the medicinal product alongside other active ingredients or combinations which have other therapeutic purposes and may or may not be protected by another basic patent in force, the fundamental objective of Regulation No 469/2009 would be undermined."

[35] "First, the holder of such a patent would enjoy only the period of effective protection conferred by the patent, which, according to the European Union legislature, is insufficient to cover the investment put into pharmaceutical

research…Second, such an approach would tend to favour monovalent medicinal products".

[36] "It is clear that such an outcome cannot be compatible with the fundamental objectives pursued by Regulation No 469/2009…"

65 Dr Selmi pointed out that even in the absence of the term "teleological" the CJEU continued to stress the importance of the fundamental objectives of the SPC Regulation when interpreting Article 3(b). Whilst the objectives of the SPC Regulation are important in its interpretation, I am not convinced by Dr Selmi's arguments that *Medeva* supports his view that the MA for DARZALEX also necessarily includes bortezomib, thalidomide and dexamethasone as active ingredients in the approved medicinal product.

66 The CJEU in *Medeva* acknowledged (at paragraphs [33]-[34]) that the development of medicinal products consisting of combinations of actives that can be administered to patients in a single preparation, such as in the form of multivalent vaccines, was a recommendation of the Health Authorities of the Member States. They went on to point out that refusal of an SPC for an innovative active ingredient or combination of active ingredients on the basis that the active(s) coexisted in the medicinal product alongside other actives would undermine the purpose of the SPC Regulation in ensuring sufficient protection to encourage pharmaceutical research and playing a role in improving public health.

67 In reaching their decision, the CJEU looked at the purpose of the SPC Regulation and found that the situation in this case corresponds with that envisaged by the Explanatory Memorandum to the SPC Regulation. Specifically, at paragraphs [37] and [38] of the judgment, the CJEU held (my emphasis):

[37] "*The requirement in Regulation No 469/2009 that the 'product' must be covered, as a medicinal product, by a MA confirms that approach in that that requirement does not in itself rule out the possibility that the MA may cover other active ingredients contained in such a medicinal product. Moreover, in accordance with Article 4 of Regulation No 469/2009, a SPC is intended to protect the 'product' covered by the MA, not the medicinal product as such*."

[38] "*Furthermore, such a situation corresponds to that described at paragraphs 34 and 39 of the explanatory memorandum, in which the Commission of the European Communities stated, first, that the requirement that the product must have obtained a valid MA is met '**if the proprietary medicinal product containing it has been granted the [MA] concerned**' and, second, that in such a situation, '**where the product authorised consists of a combination of compound X and another active ingredient, only compound X will be protected by the certificate."**"

68 In my view, the elaborate interpretation of the CJEU judgment in *Medeva* advocated by Dr Selmi is not necessary to understand the approach of the Court. It is clear that the Explanatory Memorandum, particularly at paragraphs [34] and [39], underpinned the application of the SPC Regulation by the CJEU to the facts of the case in *Medeva,* with the situation being one that had been envisaged by the SPC Regulation from its outset. Similar to the approach taken in *Farmitalia*, the CJEU

confirmed that there does not need to be a strict literal concordance between the active ingredients (or products) in the medicinal product of the MA and the active ingredients (or products) for which the SPC is sought in order to meet the objectives of the SPC Regulation. It also points to the requirements of the SPC Regulation that the active ingredients for which the SPC is sought must be covered by a MA. This interpretation of the SPC Regulation is entirely consistent with its purpose, and as set out in the Explanatory Memorandum

69 I acknowledge that each of *Farmitalia*, *Forsgren* and *Medeva* allow me to look at the purpose of the SPC Regulation when deciding what constitutes a product for the purposes of Article 3(b), with the Explanatory Memorandum providing further guidance here. However, in both *Forsgren* and *Medeva* the medicinal products for which the SPC was sought were explicitly listed as such within their respective MAs, whereas in *Farmitalia* the products were deemed to be therapeutically equivalent. So, for example where the MA for the medicinal product DARZALEX contains only the product daratumumab, the MA for the medicinal product *PEDIACEL*[29] in the case of *Medeva* comprised each of the products pertactin and filamentous haemagglutinin for which the SPC was sought, in addition to other antigens that also formed part of the medicinal product. Dr Selmi acknowledged at the hearing that DARZALEX contained only daratumumab, but he considered that, in view of the outcomes of *Farmitalia*, *Forsgren* and *Medeva* it was possible to read the MA for DARZALEX as also comprising bortezomib, thalidomide and dexamethasone as active ingredients within the medicinal product, and hence part of the product as required by Article 3(b).

70 However, I disagree with Dr Selmi's arguments that the outcome driven, "teleological" approach taken in *Farmitalia*, *Forsgren* and *Medeva* is intended to extend the reading of what constitutes the medicinal product of the MA to include active ingredients not explicitly listed as such and instead are listed as actives that fall within the therapeutic indications of the medicinal product. I can take further guidance here from the UK Courts in *Yeda* and *Newron* which have also considered what constitutes a product of a given MA. Both *Yeda* and *Newron* made clear that how a medicinal product is used does not form part of the identification of the product. It was confirmed at paragraph [19] of *Yeda* that:

> *"To my mind, it is clear from recital (10) and from the case law that what constitutes a "product" is to be strictly construed: Generics (UK) Ltd v Daiichi Pharmaceutical Co. Ltd. [2009] EWCA Civ 646, [2009] R.P.C. 23. CA. In deciding what is a "product" one must focus, as the Hearing Officer puts it, "on what the product is, rather than what it does" as the ECJ said in Case C-202/05 Yissum Research and Development Co v Comptroller-General (paragraph18):*
>
> > *"It follows that the concept of a "product" cannot include the therapeutic use of an active ingredient protected by a basic patent"."*

71 This approach in *Yeda* is consistent with the later judgment of the CJEU in *Santen* which made clear, at paragraphs [43]-[47], how the term "product" should be understood in Article 4 by reference to Article 1(b), and specifically that it should be

[29] PEDIACEL is a RTM in the UK

viewed strictly, and moreover that its use does not form part of the product definition. It was later endorsed by Birss LJ in *Newron* (at paragraph [30]). The relevant parts of paragraphs [43], [46] and [47] of *Santen* state as follows (my emphasis):

> *[43] "Moreover, it follows from a reading of Article 1(b) of Regulation No 469/2009 in conjunction with Article 4 thereof that* ***the term "product" is understood, for the purposes of applying that Regulation, to mean the active ingredient or combination of active ingredients of a medicinal product, without its being necessary to limit its scope only to one of the therapeutic applications to which such an active ingredient or combination of active ingredients may give rise*** *[…]"*
>
> *[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."***
>
> *[47] "It follows from the foregoing consideration that Article 1(b) of Regulation 469/2009 must be interpreted as meaning that* ***the fact that an active ingredient, or a combination of active ingredients, is used for the purposes of a new therapeutic application does not confer on it the status of a distinct product*** *where the same active ingredient, or same combination of active ingredients, has been used for the purposes of a different, already known, therapeutic application."*

72 In his skeleton Dr Selmi submitted that *Santen* centred on the interpretation of Article 3(d). However the Grand Chamber of the CJEU was clear that the "product" for the purposes of Article 1(b) is the same as the "product" for Article 3, so whether it is in relation to Article 3(d) as in *Santen* or 3(b), as in the present case, it is still the same[30].

73 The facts of *Yeda* and *Newron* are not wholly dissimilar to the fact of the present case. Claim 1 of *Yeda* reads:

"A therapeutic composition comprising:

(a) monoclonal antibody which inhibits the growth of human tumour cells by said antibody binding to the extracellular domain of the human EGF receptors of said tumour cells in an antigen-antibody complex, said tumour cells being characterized by their expression of human EGF receptors and mitogenic stimulation by human EGF; and

(b) a neoplastic agent

[30] It is worth noting that the Santen judgment is the first time that the Grand Chamber of the CJEU has made an explicit judgment or statement that an earlier judgment of the Court in relation to the SPC Regulation is incorrect. Furthermore, as this judgment was delivered by the Grand Chamber (of 15 judges) because of the importance of the issues being dealt with, it has to be given appropriate recognition and weight.

wherein the antibody is not antibody 108 produced by hybridoma cell line ATCC HB 9764 or antibody 96 produced by hybridoma cell line ATCC HB 9763"

whereas claim 2 reads:

"The therapeutic composition of claim 1 for separate administration of the components";

And claim 1 of *Newron* reads:

"The use of a first agent selected from safinamide from 0.5 to 1, 2, 3, 4 or 5 mg/kg/day in combination with levodopa/PDI, for the preparation of a medicament as a combined product for simultaneous, separated, or sequential use for the treatment of Parkinson's disease"

74 It is clear from the claims in *Yeda* and *Newron* that the basic patents upon which the SPC applications relied encompassed both fixed and loose combinations. The MAs in both cases, on the other hand, were to the single medicinal products- the antibody cetuximab/ERBITUX (*Yeda*), and safinamide/ XADAGO (*Newron*). The additional components that could be administered with the single medicinal products were provided in section 4.1 of the SmPC. As such these MAs were for a loose combination as in the present case. In his skeleton arguments and during the hearing Dr Selmi sought to distinguish the facts of the present case from those of *Yeda* and *Newron*. He argued that the Applicants in both *Yeda* and *Newron* could have obtained a MA for a fixed combination, because the corresponding basic patents encompassed fixed combinations. However, in the present case, the Applicant was not able to formulate the product as a fixed combination, because the basic patent only encompassed loose combinations, thus warranting a teleological approach when determining what constitutes the medicinal product of the MA. In support of this conclusion, Dr Selmi relied upon the words of Lewison J at paragraph [27] of *Yeda*:

> *"It may well have been open to the patentee to frame its application to the Community regulator for marketing authorisation in such a way as would have resulted in an authorisation for a combination of cetuximab and irinotecan. But it did not."*

And the similar point made by Birss LJ at paragraph [32] of *Newron*:

> *"It is clearly possible to conceive of a marketing authorisation of that sort, with all three of those ingredients named in combination in the decision and the SmPC as comprising the medicinal product."*

75 Dr Selmi argued that in both these cases, as their respective patents provided for a fixed combination of the active ingredients, they could have applied for a MA for a fixed combination of active ingredients, but there is no justified reason why they did not. He suggested that this was the reason that both Lewison J and Birss LJ considered that strict reading of the MAs in these cases was warranted, and further submitted that the reasoning of both Lewison J and Birss LJ "*supports the grant of an SPC in the present case because it was not open to the Applicant to frame its MA in any other way*". I disagree with Dr Selmi's interpretation. Whilst Lewison J and

Birss LJ acknowledge the possibility of obtaining a MA where the medicinal product comprised all of the actives in a fixed combination, equally they don't state that in the case where an Applicant is not able to formulate the active ingredients into a single preparation then the MA should be interpreted or construed in a manner as proposed by Dr Selmi.

76 In essence, the system that I understood Dr Selmi as proposing at the hearing was one where the Examiner would be required to first look at the basic patent and determine whether it encompasses a combination which can **only** be formulated as a loose combination, or whether it encompasses combinations which can also be formulated as a fixed combination. If the basic patent relates solely to a loose combination, such that the Applicant is not able to obtain a fixed combination MA, then a teleological approach to identifying the medicinal product in the MA is warranted. On the other hand, if the patent relates to a fixed combination or a loose combination, such that the Applicant **could** obtain a MA for a fixed combination, **even if they have not done so** then a strict reading of the MA should be adopted.

77 I cannot accept that this approach is correct as I do not agree that the Courts have established the teleological approach to MAs as asserted by Dr Selmi. As pointed out by Birss LJ in *Newron* (at paragraph [35]), the SPC scheme is meant to be relatively simple to implement. This is consistent with the Explanatory Memorandum to the SPC Regulation which states, at paragraph [16] that it '*provides for a simple, transparent system which can easily be applied by the parties concerned*'. If the approach proposed by Dr Selmi was applied in the present case, it would require an in-depth analysis of the basic patent to determine its exact scope and, in my view, would lead to difficulty and inconsistency in the application of the SPC Regulation.

78 In this respect I note that paragraph [0237] of the basic patent upon which the present SPC application relies discloses (my emphasis): *"The combination therapy of the invention may be further combined with other medicaments, i.e., combined with further therapeutic agents for the disease or condition to be treated. Such administration may be* ***simultaneous, separate, or sequential****. For simultaneous administration* ***the agents may be administered as one composition*** *or as separate compositions, as appropriate"*. When asked about this passage at the hearing, Dr Selmi submitted *"I think that is one of those patent drafting sentences to protect the position, but in reality it is very clear that the claimed combinations in this case have to be administered separately".* While that may very well be the case, in my view, this paragraph potentially indicates that the actives could be combined together in a single preparation. This highlights the potential difficulties in the system proposed Dr Selmi, and one that would not be simple and transparent as required by the SPC Regulation and as endorsed by Birss LJ in *Newron*.

79 Moreover, the system that Dr Selmi is proposing not only provides difficulty in understanding in what form the combination is disclosed in the basic patent, but it also introduces uncertainty and inconsistency into the reading of the MA, which in my view is entirely inappropriate. A teleological interpretation of the law, which could also be referred to as a purposive approach, is a legal method of interpreting the law in view of its purpose or goal rather than just the words of the law. In my opinion it cannot be appropriate to apply that approach to a regulatory document, such as a MA, not least one whose primary purpose does not include providing information for SPC purposes. Paragraph [34] of the Explanatory Memorandum to the SPC

Regulation makes clear that what is authorised to be placed on the market is what is defined in Article 1 of Directive 65/65/EEC (repealed by Directive 2001/83/EC but Article 1 remains the same) [31]), and so the product meets the requirements of Article 3(b) if the medicinal product has been granted the necessary authorisation.

80 As part of the examination process, the Examiner sought guidance from the MHRA regarding aspects of the MA approval process and the interpretation of the MA. The first question centred on MAs relating to loose combinations and what the MA holder (MAH) is allowed to place on the market. The MHRA officials confirmed that the MA of DARZALEX only allows the MA holder to place DARZALEX, i.e. daratumumab, on the market, with the referred question and answer reproduced below:

> *Question (1): "The MA relates to so-called loose combinations where the MA at section 2 of the SmPC defines a drug A and the section 4 clinical particulars of the SmPC indicate A used in combination with other drugs such as B and/or C and/or D for use in the treatment of certain conditions. It is our understanding that this sort of MA enables the marketing of A alone and that the MA holder is not allowed to place the combinations on the market using this MA. The MAH holder for A would have to seek the permission of the MAH for the other actives B or C or D to place the combinations of A with each of these other actives B or C or D to place the combinations of A with each of these other drugs on the market. Is this correct?"*
>
> *Answer: "You are correct that the MA of DARZALEX only allows the MAH to place DARZALEX on the market. The MAHs of products containing bortezomib, cyclophosphamide etc. would place these products on the market. The MAH of DARZALEX would not need to seek permission from other MAHs in order for DARZALEX to be used in combination with other products, the licensed indications and posology (including use of product with other already licensed products) reflect what was studied in clinical development."*

81 Dr Selmi argued that this does not undermine the Applicant's above submissions regarding how the MA cited in the present case should be interpreted, and pointed out that this confirms there is no other way to obtain an MA for a loose combination other than by the procedure adopted by the Applicant in this case. Indeed, the Examiner's second question and MHRA's response in this respect was as follows:

> *Question (2): "It has been suggested that the reason why the MA does not relate to a combination of daratumumab with other active ingredients is because each of these drugs is administered by a different route and, because the combination cannot be formulated as a single preparation, it is not possible to obtain a separate MA for the combination. Instead, the applicant was required to request a variation for the MA for A, having regard to regulation 1234/2008 Article 3(3). Thus, this is the <u>only</u> way that the*

[31] Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products; see CELEX Document 31965L0065; Repealed by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use; see CELEX Document 32001L0083; published in the Official Journal of the European Union L 311 28/11/2001

applicant can obtain an MA for the combination of A with B and C. Thus, it is not fair for the IPO to suggest that this MA is not for the combination- given they argue that this is the only way the combination can be licensed. Is this correct?

"*The only ways to obtain an MA for the combination would be as a fixed combination product (formulated as a combination of actives in a single preparation under reg 55 of the HMRs 2012), or exceptionally as a combination pack (a combination of active substances where the active substances are included in a separate pharmaceutical forms which are included in the same package and are covered by a single MA). Otherwise the MA is for the product with a single active e.g. DARZALEX. The MA (even with the type II variation to add an indication to specify use in combination with other active substances) is not an MA for the combination. The only way for DARZALEX to be used in combination is to specify the other active substances in the therapeutic indication, by using a variation application."*

82 The MHRA went on to confirm that it is usually not possible to obtain a MA for a combination where two (or more) actives are to be administered sequentially or in different physical forms. They also acknowledged that variations to the MA to add combination treatments would also need to be supported by new clinical efficacy and safety data, usually in the form of a phase 3 clinical trial, which are "*likely to be just as expensive, rigorous and time consuming as the original phase 3 trial to support the monotherapy*".

83 Therefore, in summary, it is clear that even in light of the additional costs and time taken for further phase 3 clinical trials, the MHRA considers that the Type II varied MA for DARZALEX only allows the MA holder to place DARZALEX on the market.

84 How the MHRA considers the MA of DARZALEX should be interpreted is, I believe, consistent with the interpretation of the MAs in *Yeda*, *Roche* and *Newron*: the MA of the medicinal product DARZALEX contains the sole active ingredient daratumumab. The MHRA was also clear that "*the MA (even with type II variation to add an indication to specify use in combination with other active substances)* ***is not an MA for the combination****"* (my emphasis). As discussed above, the active ingredients bortezomib, thalidomide and dexamethasone are listed in section 4.1 "Therapeutic indications" of the SmPC. Based on the guidance provided by the MHRA, section 4 of the SmPC specifies the **uses** for which the medicinal product, in this case DARZALEX, has been tested and deemed to be effective and provides healthcare professionals with guidance on the appropriate applications of the medicinal product. Referring again to *Santen*, and endorsed in *Newron*, it is clear that **how a medicinal product is used does not form part of the identification of the product** (my emphasis). In paragraph [35] of *Newron* Birss LJ reasoned:

"The fact there are further references to Levodopa and (a few) PDIs in the detailed parts, along with references to the clinical trials involving both, is not relevant to the very simple question what is the active ingredient in the medicinal product authorised by a given marketing authorisation"

85 This is further pithily summarised by Birss LJ at paragraph [36] of *Newron:*

"A point which emerged in argument before this court and which I believe puts the matter beyond doubt, is to focus on what exactly it is that the holder (Newron) is authorised to do as a result of the marketing authorisation in question. The answer here is that this marketing authorisation authorises Newron to market Xadago (safinamide). That is all. There is no dispute that this marketing authorisation does not authorise Newron to put on the market any other active ingredient such as Levodopa (nor other PDIs). The evidence does not address whether Newron sells Levodopa, it does not matter. However if Newron was putting Levodopa on the market at the moment there would need to be a further marketing authorisation for that."

86 Ultimately, regardless of whether MAs could have been obtained for fixed combinations, I cannot ignore the fact that both *Yeda* and *Newron* were decided on the basis that their respective MAs were for loose combinations. As in the present case, the MAs were for the single actives, with the additional active ingredients provided in Section 4.1 of the SmPC and therefore, in my view both *Yeda* and *Newron* were decided on whether the loose combination MAs were valid authorisations to place the respective combination products on the market, which I believe is analogous to the present case. Indeed, in *Newron* Birss LJ (at paragraph [36]) emphasised a point that 'puts the matter beyond doubt', and that is '*to focus on what exactly it is that the holder (Newron) is authorised to do as a result of the MA in question'.* He held that *Newron* were **only authorised to market XADAGO**, and the MA does not authorise *Newron* to place levodopa or any other actives on the market.

87 At the hearing Dr Selmi contended that there was a distinction to be made between "placing a medicinal product on the market", and "to market" said product. He pointed out that the present MA only allows the Applicant to place DARZALEX on the market, and that the respective MAs for bortezomib, thalidomide and dexamethasone are required in order to place them on the market. However, in order to "market" DARZALEX in combination with bortezomib, thalidomide and dexamethasone you would need the present Type II variation MA. Without this Type II variation MA the Applicant cannot "market" this combination treatment. As such, because the MA for DARZALEX allows it to be provided in combination with the separate active ingredients bortezomib, thalidomide and dexamethasone, Dr Selmi argues that the MA is to the loose combination of daratumumab, bortezomib, thalidomide and dexamethasone.

88 However, I do not find this argument persuasive. In my view the MA does not allow the Applicant to "market", i.e. commercialise, the combination of DARZALEX, bortezomib, thalidomide and dexamethasone as such, rather it is providing information regarding the way in which DARZALEX can be safely and effectively used in different therapeutic interventions. This is further confirmed by the MHRA in their response to the Examiner's questions (my emphasis):

"The MA (even with the type II variation to add an indication to specify use in combination with other active substances) ***is not an MA for the combination****. The only way for DARZALEX* ***to be used in combination*** *is to specify the other active substances in the therapeutic indication, by using a variation application".*

Consequently, and in line with the reasoning of Birss J in *Newron*, the MA in the present case only allows the MA holder to place DARZALEX on the market. How DARZALEX can then be used in combination therapies, as defined in Section 4.1 'Therapeutic Indications' of the SmPC is still not an authorisation to place DARZALEX on the market with bortezomib, thalidomide and dexamethasone.

89 Whilst I do not wish to downplay the large amount of effort required to obtain a Type II variation to the MA for any medicinal product in light of the additional clinical trials and efficacy and safety data are required, I do not find anything in the law that allows me to interpret the MA in the way that Dr Selmi is asking of me. Whilst I agree that in certain circumstances a teleological approach to applying the SPC Regulation is appropriate, it remains that the product itself (or a therapeutically equivalent derivative thereof) should be covered by a MA, and moreover that what constitutes the 'product' of the MA is to be interpreted strictly. As pointed out by Birss LJ in *Newron* at paragraph [30], in reference to *Santen* and taking into account the judgment of *Medeva* (my emphasis):

> *"While Newron's submission is understandable, in my judgment Medeva does not alter the law as I have found it to be from looking at the run of CJEU authority up to Santen.* ***It was a broader, outcome driven teleological approach in Neurim itself which led to the difficulty in that case*** *making it inconsistent with a run of previous authority. Santen concludes that the right approach to interpreting the SPC Regulation in the present context* ***is a strict one when one is examining what counts as the products****. Necessarily the decision also shows that while the purpose of the SPC Regulation is in turn to support the purpose of the patent system as a scheme for incentivising investment in research, nevertheless* ***not all kinds of inventions deserving of patents though they all may be, will be able to obtain an SPC****"*

Consequently, similar to the findings of Birss LJ in *Newron*, I am of the opinion that the MA only authorises the holder to place DARZALEX (daratumumab) on the market.

90 Therefore, the MA for DARZALEX (daratumumab) does not authorise the holder to put on the market any other active ingredient, such as bortezomib, thalidomide or dexamethasone. Consequently, because I have found that the MA is not a valid authorisation to place the product daratumumab, bortezomib, thalidomide and dexamethasone on the market as a medicinal product it fails to comply with Article 3(b) of the SPC Regulation.

Conclusion

91 Taking all of the above into account, I find that the marketing authorisation that forms the basis of SPC application SPC/GB20/035 in the name of Genmab A/S is not a valid authorisation to place the product applied for, namely, "daratumumab, bortezomib, thalidomide and dexamethasone", on the market as required under Article 3(b) of the SPC Regulation.

92 I also find similarly for SPC applications SPC/GB19/057, SPC/GB19/059, SPC/GB19/060, SPC/GB21/070 and SPC/GB21/071.

93 As I have found that the above SPC applications do not meet the requirements of Article 3(b) of the SPC Regulation, I refuse these applications under Article 10(2) of this Regulation.

Appeal

94 Any appeal must be lodged within 28 days after the date of this decision.

Dr Rowena Dinham

Patent Examination Group Head