Intellectual Property Office

BL O/0257/24

27 March 2024

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

APPLICANT	Halozyme, Inc.
ISSUE	Whether applications SPC/GB15/047 and SPC/GB16/039 meet the requirements of Article 3(d) of the Regulation, and whether SPC/GB15/047 meets the requirements of Article 3(c) of the Regulation
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 This decision relates to two supplementary protection certificate ("SPC") applications[1], filed in the name of Halozyme, Inc. ("the applicant"):

(i) SPC/GB15/047 for the product "*Trastuzumab and recombinant human hyaluronidase*", and

(ii) SPC/GB16/039 for the product "*Rituximab and recombinant human hyaluronidase*",.

2 SPC/GB15/047 was filed on 20 July 2015 and relies on the basic patent EP(UK) 2163643 B1 (hereafter '643 patent), entitled "*Soluble hyaluronidase glycoprotein (sHASEGP), process for preparing the same, uses and pharmaceutical compositions comprising thereof*", and the centralised European marketing authorisation EU/1/00/145/002, for the medicinal product "*HERCEPTIN*"[2]. The marketing

[1] *Of these two SPC applications, one was filed in 2015 and the other was filed in 2016. Thus, these applications and relate to the period when the UK was part of the European Union prior to its withdrawal on 31 December 2021. As such it is necessary to apply the relevant law and case law that was in force at that time in the UK. This is set out in the decision below.*

[2] *HERCEPTIN is a Registered Trademark (RTM) in the UK.*

authorisation (MA) for Herceptin was granted following Commission Implementing Decision C(2013) 5603 of 26 August 2013. Decision C(2013) 5603 granted a so-called line extension[3] to the MA, granted originally under Decision C(2000) 2539, as provided for under Commission Regulation (EC) No. 1234/2008[4].

3 SPC/GB16/039 was filed on 6 July 2016 and relies on the basic patent EP(UK) 2405015 B1 (hereafter '015 patent), entitled "*Soluble hyaluronidase glycoprotein (sHASEGP), process for preparing the same, uses and pharmaceutical compositions comprising thereof*", and the centralised European marketing authorisation EU/1/98/067/003 for the medicinal product "*MABTHERA*"[5]. The marketing authorisation (MA) for MabThera was granted following Commission Implementing Decision C(2014) 2048 of 21 March 2014. Decision C(2014) 2408 granted an extension to the marketing authorisation, granted originally under Decision C(1998) 1464 as provided for under Commission Regulation (EC) No. 1234/2008[3].

4 I note that the basic patent EP2163643 B1 on which SPC/GB15/047 relies and the basic patent EP2405015 B1 on which SPC/GB16/039 relies are both divisional applications derived from the same parent application, EP1603541 B1, which was filed on 5 March 2004, with an earliest priority date of 5 March 2003, and was granted on 6 January 2016. The expiry date of each of these patents is 4 March 2024.

5 As EU/1/00/145/002 and EU/1/98/067/003 are both authorisations granted by the European Medicines Agency (the "EMA") under the so-called centralised procedure, they each have to meet the requirements set down in Regulation (EC) 726/2004 (the "EMA Regulation") for a centralised approval that will cover all EU countries[6].

6 The applicant considers that both of these MAs relate to a product that is a combination of active ingredients and the examiner does not. This disagreement centres on the role of the human recombinant hyaluronidase component in the medicinal product and whether it can be regarded as an active ingredient or not.

7 Following several rounds of correspondence, the applicant failed to persuade the examiner on this point and the matter came before me at an oral hearing on 13 July 2023, which took place via videoconference. At the hearing the applicant was represented by Mr Thomas Mitcheson KC, barrister (hereafter referred to as Mr

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[3] *A line extension is a marketing authorisation for the same marketing authorisation holder, where, for example, the pharmaceutical form and/or strength differs from one or more other pharmaceutical products for which the applicant already holds a marketing authorisation, for further explanation see Extensions of marketing authorisations: questions and answers | European Medicines Agency (europa.eu).*

[4] *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 EUR-Lex - 32008R1234 - EN - EUR-Lex (europa.eu).*

[5] *MABTHERA is a Registered Trademark (RTM) in the UK.*

[6] *Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines agency; see EUR-Lex - 02004R0726-20190128 - EN - EUR-Lex (europa.eu).*

Mitcheson), who was instructed by Dr James Ogle, Dr Klemens Stratmann and Dr Kaspar Feldmeier of Hoffmann Eitle. Senior examiner Dr Natalie Cole acted as assistant to the hearing officer.

8 Shortly before the hearing, the Office wrote to the applicant on my behalf as the Hearing Officer dealing with the case, and asked that they be prepared to address the relevance (or not) of the recently issued *Newron*[7] decision from the Patents Court. In this context, reference was also made to the earlier *Yeda*[8] decision from the Patents court. Mr Mitcheson addressed this issue in his oral submissions at the hearing.

9 During the hearing, Mr Mitcheson stated that, although there are two SPC applications at issue in the present case, the arguments arising on each overlap significantly. For convenience and to avoid duplication, he made his arguments by reference to SPC/GB15/047 understanding that, unless specifically stated to the contrary, these arguments also applied to SPC/GB16/039. He made specific reference to SPC/GB/16/039 only when necessary. For clarity, I have followed the same approach in my decision below.

10 Following the hearing, a further written submission was sent by the applicant in relation to this case for consideration by the hearing officer. I will consider this below under "Other Matters".

11 I apologise that this decision has taken some additional time to complete to that which is usual. I thank the applicant for their patience.

Background

12 In dealing with the issues to be decided in the present case, it is helpful to keep the following details in mind regarding how the centralised approval process for human medicinal products works.

Centralised Approval of Medicinal products by European Medicines Agency (EMA)

13 In the countries of the European Union (EU)[9], medicines are granted a marketing authorisation (MA) by the European Commission so that they can be marketed and made available for human use throughout the territory of the EU member states.

14 The decision to grant the marketing authorisation is dependent on a positive recommendation from the EMA to the European Commission. This recommendation is provided as a scientific opinion from the expert Committee for Medicinal Products

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[7] *Newron Pharmaceuticals SpA v Comptroller-General of Patents, Trade Marks and Designs [2023] EWHC 1471 (Ch) (16 June 2023) (bailii.org).*

[8] *Yeda Research and Development Company Ltd v Comptroller General of Patents [2010] EWHC 1733 (Pat) (12 July 2010) (bailii.org); [2010] RPC 29*

[9] *Which included the UK at the relevant date. See also footnote 1.*

for Human Use (CHMP)[10] of the EMA which determines whether there is a suitable risk versus benefit profile for the medicinal product of interest.

15 The CHMP carries out a comprehensive scientific evaluation of the medicine based on the materials provide by the applicant and it can also ask for additional information from the applicant if necessary.

16 The CHMP examines whether the medicine meets the necessary quality, safety and efficacy requirements as set down in Directive 2001/83/EC (the Medicines Directive)[11] and determines if the proposed medicinal product offers a positive risk versus benefit balance[6].

17 The CHMP is made up of scientific experts from all EU member states and additional members with relevant expertise can be co-opted as necessary.

18 The European Commission's decision to grant a marketing authorisation is based on the CHMP opinion – without a positive opinion from the CHMP, a marketing authorisation will not be granted.

SmPC – Summary of Product Characteristics

19 As part of the evaluation process, the CHMP considers and has to approve the Summary of Product Characteristics (SmPC)[12],[13] identified and explicitly referred to in the Commission Implementing Decision granting the marketing authorisation.

20 In the present case, for example, the SmPC for Herceptin is referred to in Article 1 of Commission Implementing Decision C(2013) 5603 granting the marketing authorisation for this medicinal product. Similarly the SmPC for MabThera is referred to in Article 1 of Commission Implementing Decision C(2014) 2408 granting the marketing authorisation for this medicinal product.

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[10] For an explanation of the role of the CHMP, see EMA website at Committee for Medicinal Products for Human Use (CHMP) | European Medicines Agency (europa.eu)).

[11] 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 (the Medicines Directive). For consolidated text of Directive: see EUR-Lex - 02001L0083-20210526 - EN - EUR-Lex (europa.eu).

[12] The SmPC describes the properties and the officially approved conditions of use of a medicine. They provide the basis for the preparation of package leaflets for medicines, and so are important documents in enabling information on medicines to reach patients. The SmPC is the basis of information for healthcare professionals and patients on how to use the medicine safely and effectively. For details on how an SmPC is prepared, which it contains and how it is updated – see (i) Summary of product characteristics | European Medicines Agency (europa.eu); and (ii) A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), September 2009, Revision 2 which is included in The Rules Governing Medicinal products in the European Union, Volume 2C, Notice to Applicants at https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf.

[13] As confirmed by Article 6(1) of Regulation 726/2004 (the EMA regulation, see footnote 6), the requirements for preparation of the SmPC are those set down in Article 8(3)(j) and related Annex 1 of Directive 2001/83/EC (the Medicines Directive, see footnote 11).

21 The SmPC is drafted by the applicant and sets out the information for healthcare professionals on how to use the authorised medicinal product, and contains detailed essential information about the medicine including, among other things, its composition, dosage forms, therapeutic indications, and pharmacological details.

EPAR – European Public Assessment Report

22 After grant of the marketing authorisation by the European Commission, the EMA prepares and makes publicly available the European Public Assessment Report (EPAR)[14] for the newly authorised medicinal product. The EPAR provides detailed information about the medicine including how the active ingredients work and its assessment history.

23 The EPAR is produced from the scientific opinion prepared by the CHMP, but it will have any commercially confidential information removed.

24 Although it is not formally part of the marketing authorisation, the EPAR is derived directly from the full scientific assessment report produced by the CHMP for the EMA[15].

25 The need for the EPAR and the role of the CHMP and EMA in delivering it are specified under Article 13(3) of the EMA Regulation[6].

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[14] A European Public Assessment Report (EPAR) is published for every human (or veterinary) medicine application that has been granted or refused a marketing authorisation by the European Commission and is publicly available on the EMA website. The EPAR comprises a set of documents which detail the evaluation of a medicine authorised by the European Medicines Agency (EMA) via the centralised procedure. It comprises a series of documents and reports including: (i) a lay summary; (ii) details about the marketing authorisation holder; (iii) product information (such as the package leaflet and summary of product characteristics); and (iv) reports on the assessment carried out at the EMA. It includes information on the medicinal product, the outcomes of the clinical trials and assesses the benefits and risks associated with this medicinal product. The reports on the assessments include the scientific conclusions of the relevant EMA committee, in this case, the Committee for Medicinal products for Human Use (CHMP), providing grounds for the committee opinion to the European Commission on whether, or not, to approve an application. The EPAR is published following the assessment by the EMA of an application submitted by a pharmaceutical company seeking authorisation of the medicinal product. EPARs are published on the EMA's website, including whether the medicine they relate to was assessed positively or negatively by the EMA. For further information on purpose and contents see European public assessment reports: background and context | European Medicines Agency (europa.eu).

[15] See EMA website for further details on the procedure for centralised authorisation of medicines Authorisation of medicines | European Medicines Agency (europa.eu).

The Issue to be Decided

26 The issue to be decided in the present case is whether, as required by Article 3(d) of Regulation (EC) No 469/2009, the Medicines SPC Regulation[16,17], the marketing authorisation cited in support of application SPC/GB15/047 to the combination of trastuzumab and human recombinant hyaluronidase is the first authorisation for this combination. The same issue arises in relation to the marketing authorisation cited in support of application SPC/GB16/039 to the combination of rituximab and human recombinant hyaluronidase.

27 The answer to this question for each application turns on whether human recombinant hyaluronidase can be considered to be an active ingredient in its own right under Article 1(b) of the Medicines SPC Regulation. If it can, then the two applications at issue in the present case relate to applications for combinations of active ingredients and can proceed as such.

28 However, if human recombinant hyaluronidase is not an active ingredient as defined under article 1(b) of the Medicines SPC Regulation, then the two applications at issue in the present case will, in effect, each relate to a single active ingredient i.e. trastuzumab in the case of application SPC/GB15/047, and rituximab in the case of application SPC/GB16/039.

29 Furthermore, if human recombinant hyaluronidase is not an active ingredient as defined under article 1(b) of the Medicines SPC Regulation, then an additional issue arises in relation to application SPC/GB15/047, under Article 3(c) of the Medicines SPC Regulation, because this SPC application is not the first SPC for trastuzumab in the UK. There has already been at least one SPC granted in the UK for trastuzumab[18].

The Relevant Law

30 Article 1 of the Medicines 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:*
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> *(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*

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[16] *Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the creation of a supplementary protection certificate for medicinal products is a codification of Council Regulation (EEC) 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products (the Medicines SPC Regulation). This regulation supersedes Regulation (EEC) 1768/92 which had been amended substantially several times and codifies those changes. Annex II to Regulation 469/2009 indicates the correlation between the recitals and Articles in Regulation 1768 and those in Regulation 469/2009.*

[17] *This regulation has been assimilated into UK law since EU withdrawal in December 2021.*

[18] *See, for example, SPC/GB00/032 or SPC/GB04/015.*

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) …

The term 'active ingredient' is not defined further in the Medicines SPC Regulation.

31 Article 3 of the Medicines SPC Regulation concerns the conditions for obtaining an SPC as set out below (my emphasis in bold):

> ***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) the product has not already been the subject of a certificate;*
>
> ***(d) the authorisation referred to in point (b) is the first authorisation to place the product on the market as a medicinal product.***

32 Article 8 relates to the content of the application for a certificate, and part (b) of this Article reads as follows:

> ***1. The application for a certificate shall contain:***
>
> *(a) …*
>
> *(b)* ***a copy of the authorisation to place the product on the market****, as referred to in Article 3(b), in which the product is identified, containing in particular the number and date of the authorisation* ***and the summary of product characteristics listed in Article 11 of Directive 2001/83/EC or …****;*
>
> *(c) …;*
>
> *(d) …*

33 As we are concerned with a medicinal product for human use in this case, for the purposes of Article 3 and Article 8, the authorisation provided in support of the SPC application at issue must be one granted under Directive 2001/83/EC, the Medicines Directive[11,19].

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[19] *For details on how the authorisation system for medicines for human use works in the EU – please see guidance from European Commission in Chapter 1: Marketing Authorisation, of Volume 2A: Procedures for Marketing Authorisation, in Volume 2: the Notice to Applicants of "The Rules Governing Medicinal Products in the European Union", July 2019 updated edition – see EudraLex - Volume 2 (europa.eu).*

34 A number of procedures for authorisation of medicinal products for human use are possible under the Medicines Directive. For the purposes of the present case, we are only concerned with the centralised procedure used to provide a single marketing authorisation that was valid in all the territory of the European Union[1,20].

35 As noted already above, the EMA Regulation sets down the centralised procedure for the authorisation of medicinal products for human use at the level of the European Community and established the European Medicines Agency (EMA) as the body responsible for delivering this procedure at community level.

The Relevant Case Law

36 A number of judgements from the CJEU and UK courts are relevant to the present case.

37 The following CJEU judgements which refer to Article 1 and Article 3 of the Medicines SPC Regulation are helpful in determining what is an active ingredient for the purposes of the Medicines SPC Regulation:

(i) C-431/04 Massachusetts Institute of Technology ("*MIT*")[21]

(ii) C-210/13 GlaxoSmithKline Biologicals SA and GlaxoSmithKline Biologicals, Niederlassung der Smithkline Beecham Pharma Gmbh & Co. KG v Comptroller General of Patents, Designs and Trade Marks ("*GSK*")[22]

(iii) C-631/13, Arne Forsgren v. Österreicheisches Patentamt ("*Forsgren*")[23]

38 In addition, a further CJEU judgement which concerns the plant protection product (PPP) SPC regulation[24] is also relevant to the present case:

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[20] As both of the SPC applications that are the subject of the present case relate to the period before the withdrawal of the UK from the European Union at the end of 2021, a central authorisation granted under the EMA Regulation approved the placing on the market in the UK of the respective medicinal products.

[21] For full text of the MIT CJEU decision see ECLI identified: ECLI:EU:C:2006:291; CJEU - Judgment C-431/04 Massachusetts Institute of Technology 4 May 2006 (ipcuria.eu).

[22] For full text of the GSK CJEU decision see CURIA - Documents (europa.eu).

[23] For full text of the Forsgren CJEU decision see ECLI identifier ECLI:EU:C:2015:13 CURIA - Documents (europa.eu).

[24] 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; CELEX Document number: 31996R1610; published in Official Journal of the European Union L 198 on 08.08.1996, see EUR-Lex - 31996R1610 - EN - EUR-Lex (europa.eu).

(iv) C-11/13, Bayer Crop Science AG v. Deutsches Patent- und Markenamt ("*Bayer*")[25]

39 The decision of the UK Patents Court following the return of the *Abraxis* case form the CJEU is also relevant, see:

(v) Abraxis Bioscience LLC v. The Comptroller-General of Patents [2017] EWHC 14 (Pat) ("*Abraxis UK*")[26]

40 I have summarised the key points from these cases below.

MIT (C-431/04)

41 The *MIT* case concerned the medicinal product "Gliadel", a combination of polifeprosan, a polymeric, biodegradable excipient, and carmustine, an active ingredient used in the treatment of brain tumours. Gliadel is implanted into the cranium where the polifeprosan, acts as a bio-erodible matrix which slowly and gradually releases the carmustine.

42 The decision focussed on the meaning of "active ingredient". The BundesPatentGericht (BPG, Federal Patent Court of Germany) made a reference to the CJEU for a preliminary ruling on the interpretation of Article 1(b) of the Regulation. Two questions were referred to the Court:

(1) Does the concept of "combination of active ingredients of a medical product" within the meaning of Article 1(b) of Regulation [No 1768/92] mean that the components of the combination must all be active ingredients with a therapeutic effect?

(2) Is there a "combination of active ingredients of a medicinal product" also where a combination of substances comprises two components of which one component is a known substance with a therapeutic effect for a specific indication and the other component renders possible a pharmaceutical form of the medicinal product that brings about a changed efficacy of the medicinal product for this indication (in vivo implantation with controlled release of the active ingredient to avoid toxic effects)?

43 The CJEU found that "active ingredient" does not include substances forming part of a medicinal product which do not have an effect of their own on the human or animal body. In doing so, the Court drew attention to point 11 of the Explanatory Memorandum (my emphasis added in bold):

> *"The proposal for a Regulation therefore concerns only new medicinal products.* ***It does not involve granting a [SPC] for all medicinal products that are authorised to be placed on the market****. Only one [SPC] may be granted for any one product, a product being understood to mean an active*

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[25] For full text of the Bayer CJEU decision: see ECLI identifier: ECLI:EU:C:2014:2010; CURIA - Documents (europa.eu); EUR-Lex - 62013CJ0011 - EN - EUR-Lex (europa.eu).

[26] For full text of the Abraxis decision from the UK Patents Court: see Abraxis Bioscience LLC v The Comptroller-General of Patents [2017] EWHC 14 (Pat) (13 January 2017) (bailii.org)).

substance in the strict sense. Minor change to the medicinal product such as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the issue of a new [SPC]"

44 The Court concluded at paragraph 25 that:

> *"In light of the foregoing, the inevitable conclusion is that a substance which does not have any therapeutic effect of its own and which is used to obtain a certain pharmaceutical form of the medicinal product is not covered by the concept of "active ingredient", which in turn is used to define the term "product"."*

and further stated, at paragraphs 27-29, that:

> *"27. The fact that the substance without any therapeutic effect of its own renders possible a pharmaceutical form of the medicinal product necessary for the therapeutic efficacy of the substance which does have therapeutic effects cannot invalidate that interpretation.*
>
> *28. …it is apparently not unusual for substances which render possible a certain pharmaceutical form of the medicinal product to influence the therapeutic efficacy of the active ingredient contained in it.*
>
> *29. Thus, a definition of "combination of active ingredients of a medicinal product" which includes a combination of two substances, only one of which has therapeutic effects of its own for a specific indication, the other rendering possible a pharmaceutical form of the medicinal product which is necessary for the therapeutic efficacy of the first substance for that indication, might, on any view, create legal uncertainty in the application of Regulation No 1768/92, as the French Government pointed out at the hearing. Whether a substance without any therapeutic effect of its own is necessary for the therapeutic efficacy of the active ingredient cannot, in this case, be regarded as a sufficiently precise test.*

45 Thus, the decision of the CJEU in *MIT* makes clear that the meaning of "active ingredient" does not include substances forming part of the medicinal product which do not have an effect of their own on the human or animal body. This is the case even where a substance, while not having therapeutic efficacy of its own for a specific indication, makes possible a pharmaceutical form which is necessary for the therapeutic efficacy of the first substance for a specific therapeutic indication.

46 For the purposes of the present case, I also note also that this judgement does also point out (see para 29 above) that to be included in a combination of active ingredients, the component of interest has to show that it "has therapeutic effects of its own for a specific indication". Thus it is not just enough to have any therapeutic effect; it has to be for the specific indication of interest.

GSK (C-210/13)

47 The referring Court in *GSK* sought further clarification form the CJEU on the interpretation of "active ingredient" within the meaning of Article 1(b). *GSK* related to

two SPC applications, the first to the product "*an oil in water emulsion comprising squalene, DL-a-tocopherol and polysorbate 80*", which is an adjuvant for use with vaccines and is also known as AS03, and the second to a pandemic influenza vaccine containing the AS03 adjuvant. Two questions were referred to the Court:

> *(1) Is an adjuvant which has no therapeutic effect on its own, but which enhances the therapeutic effect of an antigen when combined with that antigen in a vaccine, an "active ingredient" within the meaning of Article 1(b) of Regulation (EC) No 469/2009?*
>
> *(2) If the answer to question 1 is no, can the combination of such an adjuvant with an antigen nevertheless be regarded as a "combination of active ingredients" within the meaning of Article 1(b) of Regulation (EC) No 469/2009?*

48 In its decision, the CJEU followed the judgement in *MIT* (see above), concluding that because the adjuvant has no therapeutic effect of its own, it cannot be regarded as an active ingredient within the meaning of Article 1(b) of the Regulation.

49 Further, the CJEU drew on the distinction made between "active ingredient" and "adjuvant" in Annex I of Directive 2001/83/EC, as amended by Directive 2003/63/EC (paragraphs 36-38 of the judgment) which states as follows (my emphasis added in bold):

> *36. That distinction between "active ingredient" and "adjuvant" is also made quite clear in section 3.2.2.1 of Part 1, entitled "Standardised marketing authorisation dossier requirements", of Annex I to Directive 2001/83, as amended by Directive 2003/63. That annex lists the particulars and documents to be submitted in support of an MA application in accordance, inter alia, with Article 8(3) of the Directive, as amended.*
>
> *37. Section 3.2.2.1 states as follows:*
>
> > *"A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:*
> >
> > - ***The active substance(s),***
> > - ***The constituent(s) of the excipients, whatever their nature*** *or the quantity used, including colouring matter, preservatives,* ***adjuvants****, stabilisers, thickeners, emulsifiers, favouring and aromatic substances, etc.,*
> > - *The constituents, intended to be ingested or otherwise administered to the patients, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.)"*
>
> *38. Thus, in Directive 2001/83, amended by Directive 2003/63, the concepts of "active substance" and "adjuvant" are clearly distinct and that also holds,*

in the context of Regulation No 469/2009, for the concept of "active ingredient", which cannot, as such, include an adjuvant.

50 The CJEU made clear that because the concepts of "active ingredient" and "adjuvant" in Directive 2001/83/EC, as amended by Directive 2003/63/EC, are distinct, the same is true in the context of Regulation No 469/2009, that is, the meaning of "active ingredient" does not include "adjuvant".

Forsgren (C-631/13)

51 The *Forsgren* case concerned the use of Protein D, an IgD-binding protein of *Haemophilus influenzae*, as a carrier protein in a pneumococcal vaccine for paediatric use, named "Synflorix". The Board of Appeal of the Österreichisches Patentamt noted the therapeutic effect of Protein D against the Haemophilus influenzae bacterium. However, it found that Protein D was not present as such in Synflorix but was used solely to carry and covalently bond other active ingredients. Three questions were referred to the CJEU:

(1) Is grant of an SPC precluded on the sole ground that the active ingredient is covalently bound to other active ingredients?

(2) (a) whether grant of an SPC is precluded for an active ingredient whose therapeutic effect does not fall within the therapeutic indications covered by the wording of the marketing authorisation; and

(2) (b) whether a carrier protein conjugated to a pneumococcal polysaccharide used in a vaccine for a paediatric use may be regarded as a "product" within the meaning of the Regulation, i.e. as an active ingredient or combination of active ingredients.

52 In answering question (1), the CJEU, noting, in para 24, that the term 'active ingredient' is not defined in the Medicines SPC Regulation, referred to the updated definition of 'active substance' in Article 1 of Directive 2001/83, as amended by Directive 2011/62/EU in June 2011. The CJEU noted that 'active substance' has the same meaning as "active ingredient" and is defined as:

"any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis".

As a consequence, the CJEU noted (in following paras 25 & 26) that.

"It follows that the term 'active ingredient', for the purposes of applying Regulation No 469/2009 (the SPC Regulation), concerns substances producing a pharmacological, immunological or metabolic action of their own."

and, referring to the earlier CJEU judgment in *MIT* (see above and para 25 of the *MIT* judgment itself), the CJEU in *Forsgren* also noted:

> *"… that a substance which has no therapeutic effect of its own and which is used to obtain a certain pharmaceutical form of the medicinal product is not covered by the term 'active ingredient' and, consequently, cannot give rise to the grant of an SPC."*

53 In the operative part of the CJEU judgement (reproduced below) it makes clear that finding a "*pharmacological, immunological or metabolic action of its own*" is not the only requirement, this action must be in relation to the therapeutic indications of the marketing authorisation (my emphasis added in bold):

> *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 is established that it produces a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indications 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.***

Bayer (C-11/13)

54 In contrast to the above mentioned CJEU cases which all related to the Medicinal products SPC regulation, the *Bayer* case concerned a plant protection product covered by the PPP SPC Regulation No 1610/96[24,27]. Although the latter is closely related to the Medicines SPC Regulation, the system for granting SPCs under each of these regulations, while it has many similarities, is not the same[28]. The conditions and procedures for grant of authorisation to place plant protection products on the market ('MA') in the European Union and for their subsequent review and withdrawal were established by Directive 91/414/EEC[29] which, since 14 June 2011 has been superseded and repealed by Regulation 1107/2009[30]. For the purpose of the *Bayer* case, Directive 91/414/EEC was the operative legislation.

55 The types and roles of the products that are used for plant protection are different to those that are used for treatment of illness in humans (and animals), as illustrated, by the definitions set down in Article 1 of the PPP SPC regulation and Article 1 of the

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[27] The PPP SPC regulation has been assimilated into UK law since EU withdrawal in December 2021.

[28] Directive 91/414/EEC concerning the placing of plant protection products on the market (OJ 1991 L 230, p. 1), as amended by Commission Directive 2006/136/EC of 11 December 2006 (OJ 2006 L 349, p. 42).

[29] See Article 2 of Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market.

[30] Regulation (EC) No. 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.

Medicines SPC regulation and by the approval system outlined by Directive 91/414/EEC compared to that outlined by the Medicines Directive.

56 This case was particularly referred to by the applicant and their attorney in their submissions before the hearing and by counsel for the applicant at the hearing itself.

57 As Article 3(1) of Directive 91/414/EEC makes clear, plant protection products cannot be placed on the market and used in a Member State unless the competent authorities of that State have authorised the product in accordance with the two-stage process set out in this directive.

58 In this case, the court, taking note of Directive 91/414/EEC and the PPP SPC Regulation 1610/96, considered what is the nature of the "active substance" for the purposes of a plant protection product and set matters out as follows in paras 29-33 (my emphasis added in bold):

> *"29. Article 2 of Regulation No 1610/96 provides that '[a]ny product protected by a patent in the territory of a Member State and subject, prior to being placed on the market as a plant protection product, to an administrative authorisation procedure as laid down in Article 4 of Directive [91/414], or pursuant to an equivalent provision of national law if it is a plant protection product in respect of which the application for authorisation was lodged before Directive [91/414] was implemented by the Member State concerned, may, under the terms and conditions provided for in this Regulation, be the subject of a certificate'.*
>
> *30. The term 'product' is defined in Article 1.8 of Regulation No 1610/96 as being 'the active substance … or combination of active substances of a plant protection product'.*
>
> *31. As regards 'active substances', they are themselves defined in Article 1.3 of that regulation as 'substances or micro-organisms including viruses, having general or specific action … against harmful organisms … or … on plants, parts of plants or plant products'.*
>
> *32. The term 'active substances' is used in Article 1.1 of that regulation to define the term 'plant protection products'. That provision refers to the uses for which the active substances included in the composition of plant protection products are intended. Under that provision, those uses may be to 'protect plants or plant products against all harmful organisms or prevent the action of such organisms, … [to] influence the life processes of plants, other than as a nutrient (e.g. plant growth regulators), …[to] preserve plant products, …[to] destroy undesirable plants, or [to] destroy parts of plants, [to] check or [to] prevent undesirable growth of plants'.*
>
> *33.* ***It follows from the above that the term 'active substances', for the purposes of the application of Regulation No 1610/96, relates to substances which have a toxic, phytotoxic or plant protection action of their own. In this regard, since Regulation No 1610/96 makes no distinction according to whether that action is direct or indirect, there is no need to restrict the term 'active substances' to those whose***

action may be characterised as direct *(see by analogy, so far as concerns pharmaceutical products, Chemische Fabrik Kreussler, C-308/11, EU:C:2012:548, paragraph 36, and, as regards biocidal products, Söll, EU:C:2012:111, paragraph 31).”*

59 Having looked at what can be constituted an active substance, the CJEU then considered what is not an active substance and at that point drew an analogy with the situation for “active ingredients” in medicinal products. Drawing support from the CJEU decision in *MIT* (see above), the CJEU concluded, in para 34, that a substance that does not have a toxic, phytotoxic or plant protection action cannot be considered to be an ‘active substance’ in a plant protection product covered by the Plant Protection Product SPC Regulation No 1610/96, setting its conclusion out as follows (my emphasis added in bold):

“34. Conversely, a substance with no such toxic, phytotoxic or plant protection action cannot be considered to be an ‘active substance’ within the meaning of Regulation No 1610/96 and, consequently, cannot give rise to the issue of a supplementary protection certificate*. **That interpretation corresponds to that applied in respect of medicinal products, the Court already having had the opportunity to hold that a substance with no pharmaceutical effects of its own, such as an excipient or an adjuvant, does not constitute an active ingredient and, consequently, cannot give rise to the grant of a supplementary protection certificate** (Massachusetts Institute of Technology, EU:C:2006:291, paragraph 25, and order in GlaxoSmithKline Biologicals and GlaxoSmithKline Biologicals, Niederlassung der Smithkline Beecham Pharma, C-210/13, EU:C:2013:762, paragraph 35).*

35. The answer to the question whether a safener is an active substance, within the meaning of Article 1.3 of Regulation No 1610/96, therefore depends on whether that substance has a toxic, phytotoxic or plant protection action of its own. If that is the case, it falls within the concept of a ‘product’, within the meaning of Article 1.8 of that regulation and may therefore, provided the conditions set out in Article 3 of Regulation No 1610/96 are observed, give rise to the issue of a supplementary protection certificate*.*

36. It is apparent from the explanations provided by the referring court and the observations submitted by Bayer and the Commission that safeners contained in the composition of plant protection products are intended to reduce the toxic effects of those products on certain plants. Safeners may thereby increase the effectiveness of a plant protection product by improving its selectivity and by limiting its toxic or ecotoxic effects.”

However, while confirmation that the substance has a toxic, phytotoxic or plant protection action of its own is necessary, it is not sufficient for the grant of a plant protection product SPC.

60 In addition, the four requirements set down in Article 3(1) of the Plant Protection Product SPC Regulation must be fulfilled. These four requirements mirror the same

four requirements set down in Article 3 of the Medicines SPC regulation; i.e. a plant protection product SPC cannot be granted unless, at the date of the application:

(a) the product is protected by a basic patent in force;
(b) the product has not already been the subject of a certificate;
(c) the medicinal product is the subject of a valid MA approved '*in accordance with Article 4 of Directive [91/414] or an equivalent provision of national law'*, and
(d) that this MA is the first authorisation to place the product on the market as a plant protection product.

MAs for plant protection products are granted in a two-stage process where the active substance is approved first and then commercial formulations with this active substance are subsequently approved nationally – taking into account the geographical zone in which it will be used. Thus, MAs for plant protection products are granted nationally. There is no centralised system for granting marketing authorisations for plant protection products in the same way as there is for medicinal products. As a consequence, the CJEU noted (at para 40) that:

> "*it is therefore for the national court before which the dispute has been brought to ascertain whether, as provided in Article 3 of Regulation No 1610/96, the product containing the safener at issue in its composition has, on the territory of the Member State concerned, a valid MA as a plant protection product 'in accordance with Article 4 of Directive [91/414]"*

Furthermore, the CJEU noted (at para 42) that (my emphasis added in bold):

> "*while Directive 91/414 is not without importance for the application of Regulation No 1610/96,* ***the grant of a supplementary protection certificate is still regulated autonomously by that regulation****"*.

61 Thus the court has made clear that the key question to be answered by the national courts when deciding if an SPC can be granted for a substance which has an action of its own is determining if the substance in question has been the subject of a dossier demonstrating the effectiveness and effects of the plant protection product containing that substance and, if as a consequence, of this approval process, the applicant has been delayed in being able to exploit their patent.

62 In answer to this the CJEU noted that, although no safener was included in Annex I to Directive 91/414 (which comprises the list of all active substances that have been approved for use in plant protection products), that fact, in and of itself, did not lead to the definite conclusion that the commercial exploitation of a patent for a safener <u>has not been delayed</u> on account of the time required to obtain an MA *"in accordance with Article 4 of Directive [91/414]* …" as is required under Article 3 of Plant Protection Product SPC Regulation.

63 Thus, at paras 43 and 44 of this judgement, the CJEU, provided the following guidance to the national court (my emphasis added in bold):

> "*43. The procedure for an MA referred to in Article 4 of Directive 91/414 requires the submission of the dossier provided for in Annex III to that directive and intended to demonstrate, in particular, the effectiveness and*

the effects of a plant protection product. ***That dossier must include, in particular, data concerning the co-formulants referred to in point 1.4.4 of Part A of Annex III, among which safeners are included. Therefore, it is possible that the submission of a dossier in accordance with the requirements set in Annex III with a view to obtaining an MA for a plant protection product containing a safener has delayed the commercial exploitation of a patent for that safener.***

44. In that regard, the referring court stated specifically that Isoxadifen was examined in connection with a procedure for a provisional MA for a product containing two other active substances ***and that the duration of that procedure reduced the effective duration of protection provided by the patent****. Those matters, should they be established by the national court before which the case in the main proceedings has been brought, which alone has jurisdiction in this respect, may enable that court to consider the condition set out in Article 3 of Regulation No 1610/96 and relating to the existence of a valid MA obtained in accordance with Article 4 of Directive 91/414 to be fulfilled.****"***

64 Thus, although not explicitly identified as such, under the definition of the term 'product' in Article 1.8 and Article 3(1) of Regulation (EC) No 1610/96, and the term 'active substances' in Article 1.3 of this regulation, those terms can include a substance intended to be used as a safener in a plant protection product but only when it is established that these have a material effect on the duration of the approval process, where that substance has been determined to have a toxic, phytotoxic or plant protection action of its own in the context of the plant protection product that is being approved.

Abraxis UK

65 This decision of the UK High Court concerned an appeal by *Abraxis* following the refusal by the Intellectual Property Office to grant an SPC for the product "*Paclitaxel formulated as albumin bound nanoparticles*" also referred to as nab-paclitaxel. This product was comprised of nanoparticles of paclitaxel coated with albumin in a manner which resulted in both components being transported across the cell membrane as a single unit. Nab-paclitaxel demonstrated greater efficacy than paclitaxel for treating certain tumours.

66 The Court held that nab-paclitaxel was not an active ingredient within the meaning of Article 1(b) of the Medicines SPC Regulation: paclitaxel being the active ingredient and albumin acting as the carrier. Mr Justice Arnold considered that no further guidance from the CJEU was needed as to the interpretation of Article 1(b) since the interpretation of that provision was *acte clair* (although he did refer a question concerning Article 3(d) of the Regulation). The CJEU judgements in *MIT*, *GSK* and *Forsgren* had made it clear that Article 1(b) should be interpreted strictly and cannot include substances that do not have a therapeutic effect of their own. Mr Justice Arnold noted, at paragraph 18 of the judgement, that while "*active ingredient*" is not defined in the Medicines SPC Regulation, a strict interpretation is supported by the Commission's Explanatory Memorandum for Council Regulation 1768/92/EEC which stated, at paragraph 11:

"The proposal for a Regulation therefore concerns only new medicinal products. It does not involve granting a certificate for all medicinal products that are authorized to be placed on the market. Only one certificate may be granted for any one product, a product being understood to mean an active substance in the strict sense. Minor changes to the medicinal product such as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the issue of a new certificate".

ARGUMENT AND ANALYSIS

Argument

67 I will summarise the main points made in the arguments presented by the examiner and the applicant, before presenting my analysis and conclusions regarding the issues to be decided.

Views of Examiner

68 Throughout the examination process the examiners dealing with the respective cases each maintained their view that recombinant human hyaluronidase (rHuPH20), listed in the product definition for SPC/GB15/047 and SPC/GB16/039, cannot be considered an active ingredient within the meaning of Article 1(b) of the Medicines SPC Regulation. This is because, in applying the relevant case law (see above), neither the SmPC that accompanies the marketing authorisation, nor the related EPAR, showed that recombinant human hyaluronidase has the same pharmacological, immunological or metabolic effect as the identified active ingredient trastuzumab (see SPC/GB15/047 application) or rituximab (see SPC/GB16/039 application).

69 It is the examiner's opinion that, whilst rHuPH20 has an effect on the body, it is not an effect on the medical condition that trastuzumab (SPC/GB15/047) and rituximab (SPC/GB16/039) were approved for in the respective marketing authorisations supporting these applications. Consequently, as rHuPH20 cannot be considered to be an active ingredient under the meaning of Article 1(b), it is the examiner's view that the medicinal product at issue for SPC/GB15/047 is actually trastuzumab alone and for SPC/GB16/039 is actually rituximab alone. As such, an SPC cannot be granted in each of cases because trastuzumab and rituximab have previously already been the subject of earlier marketing authorisations (EU/1/00/145 and EU/1/98/067, respectively). As a result, they do not meet the requirement of Article 3(d) of the Medicines SPC Regulation.

70 Furthermore, in relation to SPC/GB15/047, the examiner considered that this SPC application also does not comply with Article 3(c) of the Regulation because, at least, one earlier supplementary protection certificate for trastuzumab has been granted in the UK[18].

Views of Applicant

71 The applicant does not agree with the examiner's conclusions, particularly in relation to the examiner's interpretation of the relevant case law with respect to Article 1(b) of the Medicines SPC Regulation.

72 The applicant submits that recombinant human hyaluronidase (rHuPH20) has indirect and direct effects on the body relevant to the particular treatments of cancer indicated in the respective marketing authorisations. This was illustrated by reference to some of the clinical studies referred to in the respective MA and was supported by reference to the basic patent and some of the scientific publications cited therein. As such, the applicant contends that rHuPH20 meets the definition of product in Article 1(b) (as a combination of active substances) and therefore meets the requirements of Articles 3(d) and 3(c).

Analysis

73 As I have outlined above, the applicant considers that each of the MAs in question relate to a product that is a combination of active ingredients and the examiner does not. The disagreement between both centres on what significance they attach to role played by human recombinant hyaluronidase in the medicinal product. The examiner focuses very clearly on the medicinal product and what the SmPC says about it and the role of the human recombinant hyaluronidase component which is not the same as the role of the trastuzumab component or the rituximab component. The applicant considers that this is too literal or narrow a view and that one should consider all the information that is available in the application in relation to the human recombinant hyaluronidase component and directed me to consider what is in the patent – either directly or by reference - as well as what is in the marketing authorisation.

74 As already noted, the decision to grant an SPC is an autonomous one under the SPC regulation and it involves an assessment of all the requirements under Article 3. In the present case, the issue that arises is under Article 3(d) and so to deal with this question it is necessary to examine the authorisation that is cited in support of the present application. Therefore, as a first step, I will look at the marketing authorisations that have been provided in support of the present SPC applications to determine what is the product, as defined under Article 1(b) of the Medicines SPC regulation, which is present in each of these medicinal products.

The Marketing Authorisations (MAs) cited in support of SPC/GB15/047 and SPC/GB16/039

75 The marketing authorisation for a medicinal product is made up of the Commission implementing decision and the associated Annexes I-III referred to in that decision[31,32].

76 If, as in this case, there has been a line extension to the original marketing authorisation, this will necessitate a further Commission implementing decision and amendment of the respective Annexes, including the SmPC, to include all the details of the line extension. Table 1 below identifies the different physical forms (i.e., the original physical form and subsequent line extensions) that have been approved for each of the medicinal products of interest in this case – the line extension for Herceptin that includes hyaluronidase is highlighted in yellow and that for MabThera is highlighted in green. In both cases, we are concerned with the newest formulation or physical form of the respective medicinal products, i.e. those that have been developed for administration as a subcutaneous injection.

77 In my discussion below, I use the term Herceptin SC to refer to the subcutaneous injection formulation and Herceptin IV to refer to the original formulation for intravenous administration.

The HERCEPTIN Marketing Authorisation

78 The MA provided in support of SPC/GB15/047 is a so-called line extension to the Herceptin marketing authorisation to include a new route of administration (subcutaneous injection) which is delivered with a new strength (1400 mg) and in a new pharmaceutical form, as a solution for injection – this is identified in the updated and amended SmPC for the MA as EU/1/001/145/002.

79 The marketing authorisation for Herceptin was originally granted following Commission Implementing Decision C(2000) 2539 for a different pharmaceutical form of Herceptin, i.e., 150 mg powder for concentrate for solution for infusion, i.e., powder to make up solution for delivery by intravenous infusion, identified as EU/1/001/145/001. The human recombinant hyaluronidase is not present in the original physical form of Herceptin authorised by EU/1/001/145/001 but is present in the further physical form of Herceptin authorised as EU/1/001/145/002. Thus the Human recombinant hyaluronidase is only relevant for the physical form that is used for subcutaneous injection (see Table 1).

80 The marketing authorisation for Herceptin cited in support of SPC application SPC/GB15/047 was granted following Commission Implementing Decision C(2013)

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[31] Annex I to the Commission implementing decision is the Summary of Product Characteristics (SmPC); Annex II provides the details of the Manufacturers of the Active Substance and the Conditions and Restrictions for Supply & Use and Annex III is the Labelling and Packaging Information. See discussion, for example, in IPO decision BL O/1053/22 concerning Newron's SPC application (see paras 33-47, but especially 25-37).

[32] For further details of the Annexes to the Commission Implementing Decision and their purpose and role - see EMA website, for example, Marketing authorisation | European Medicines Agency (europa.eu).

5603 of 26 August 2013 which approved the changes to the marketing authorisation originally approved by Decision C(2000) 2539. This followed the positive recommendation from the CHMP at the EMA that the MA could be extended. As indicated in the updated SmPC, and as confirmed by the EPAR (which includes the assessment report from the CHMP on the application for the line extension)[33], this new physical form is approved for use in some of the same treatments as the original physical form, i.e. early breast cancer.

References to Hyaluronidase in the Summary of Product Characteristics (SmPC)

81 The amended and updated SmPC annexed to Decision C(2013) 5603 identified human recombinant hyaluronidase as an excipient – see in particular (my emphasis added in bold):

(i) Section 6.1, 'List of Excipients' (page 52) - which lists *"**Recombinant human hyaluronidase (rHuPH20)***" as the first of 7 excipients;

Furthermore, I note that hyaluronidase is consistently referred to in this manner throughout the SmPC, see for example:

(ii) Section 4.3: Contraindications (page 31) - which refers to "*hypersensitivity to trastuzumab, murine proteins, **hyaluronidase or to any of the other excipients listed in section 6.1***".

(iii) Section 4.8: Undesirable Effects: Description of selected adverse reactions with the subcutaneous formulation (page 40) - which refers to "*15.3 % of patients treated with Herceptin subcutaneous formulation developed antibodies against **the excipient hyaluronidase (rHuPH20)**. The clinical relevance of these antibodies is not known*."

82 The SmPC also discloses the purpose of the hyaluronidase in the formulation stating that (my emphasis added in bold and underline):

> *"Herceptin subcutaneous formulation contains recombinant human **hyaluronidase** (rHuPH20), an enzyme used **to increase the dispersion and absorption of co-administered drugs when administered subcutaneously***".

83 In 'Section 5.3: Pre-Clinical Safety Data (page 52)' which considers both the Intravenous Formulation and Subcutaneous Formulation, the SmPC confirms that the presence of the hyaluronidase excipient did not have an adverse impact on the role of Herceptin, i.e. (my emphasis added in bold):

> "Subcutaneous formulation
>
> *A single dose study in rabbits and a 13-week repeat dose toxicity study in Cynomolgus monkeys were conducted. The rabbit study was performed to specifically examine local tolerance aspects. **The 13-week study was***

[33] *Identified as procedure number EMEA/H/C/000278.*

Table 1: Different physical forms of the medicinal products ***HERCEPTIN*** and ***MABTHERA*** authorised for human use as disclosed in the respective marketing authorisations (see respective EPAR for authorised presentations).

Medicinal Product	EMA Number	Active Substance	Strength	Pharmaceutical Form	Route of Administration	Content (concentration)	Pack size	Excipients (see section 6.1, SmPC)
HERCEPTIN	EU/1/00/145/001	trastuzumab	150 mg	Powder for concentrate for solution for infusion	Intravenous (IV) use	150 mg	1 vial (glass)	L-histidine hydrochloride L-histidine α,α-trehalose dihydrate Polysorbate 20
	EU/1/00/145/002	trastuzumab	600 mg	***Solution for injection***	***Subcutaneous (SC) use***	5 ml	1 vial (glass)	L-histidine L-histidine hydrochloride monohydrate α,α-trehalose dihydrate Polysorbate 20 ***Recombinant human hyaluronidase (rHuPH20)*** L-methionine Water for injections
MABTHERA	EU/1/98/067/001	rituximab	100 mg	Concentrate for solution for infusion	Intravenous (IV) use	10 ml (10 mg/ml)	2 vials (glass)	Sodium citrate, Polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.
	EU/1/98/067/002	rituximab	500 mg			50 ml (10 mg/ml)	1 vial (glass)	
	EU/1/98/067/003	rituximab	1400 mg	***Solution for injection***	***Subcutaneous (SC) use***	11.7 ml (120 mg/ml)	1 vial (glass)	Polysorbate 80 Water for injections ***Recombinant human hyaluronidase (rHuPH20)*** L-histidine L-histidine hydrochloride monohydrate α,α-trehalose dihydrate L-methionine
	EU/1/98/067/004	rituximab	1600 mg			13.4 ml (120 mg/ml)	1 vial (glass)	

performed to confirm that the change in route of administration and the use of the novel excipient recombinant human hyaluronidase (rHuPH20) did not have an effect on the Herceptin safety characteristics. Herceptin subcutaneous formulation was locally and systemically well tolerated*.*

Hyaluronidase *is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. ….*"

84 The SmPC (see Section 5.1, 'Pharmacodynamics properties' (page 41)) also discloses the purpose of the hyaluronidase in the formulation which relates to how it is administered, i.e. subcutaneously; stating (my emphasis added):

> "*Herceptin subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20),* ***an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously****."*

85 The EPAR for Herceptin also indicates that the hyaluronidase is acting as an excipient, see:

(i) Section 2 – Scientific discussion; Sub-section 2.1 – Introduction; page10:
"*The SC administration of trastuzumab* ***is enabled by the use of recombinant human hyaluronidase*** *(rHuPH20),* ***a key excipient in the trastuzumab SC formulation which acts as a permeation enhancer****."*

(ii) Section 2 – Scientific discussion; Sub-section 2.2 – Quality Aspects; Sub-sub-section 2.2.3 - Finished Medicinal Product; page12:
"The finished product formulation consists of 120 mg/mL trastuzumab in L-histidine/histidine hydrochloride buffer, trehalose dihydrate, methionine, rHuPH20, and polysorbate 20. ***rHuPH20 is a recombinant human hyaluronidase which allows the subcutaneous injection of large volumes****.* ***rHuPH20 is considered a novel excipient.****"*

(iii) Section 2 – Scientific discussion; Sub-section 2.2 – Quality Aspects; Sub-sub-section 2.2.3 - **Novel Excipient (rHuPH20):** page 13:
"The rHuPH20 degrades hyaluronan under physiological conditions and acts as a spreading factor in vivo. Thus, when combined or co-formulated with certain injectable drugs, ***rHuPH20 facilitates the absorption and dispersion of these drugs by temporarily clearing a path through the connective tissue in the subcutaneous space****."*

(iv) Section 2 – Scientific discussion; Sub-section 2.2 – Quality Aspects; Sub-sub-section 2.2.3 - Specification**:** page 14:
"The proposed specification for rHuPH20 is considered adequate to confirm the high quality of the ***excipient****."*

(v) Section 2 – Scientific discussion; Sub-section 2.2 – Quality Aspects; Sub-sub-section 2.2.4 - Discussion on chemical, pharmaceutical and biological aspects: Quality Development: page 15;
*"Appropriate general information about the **novel excipient rHuPH20** has been provided. The potency assay is adapted from the USP method for activity……."*

(vi) Section 2 – Scientific discussion; Sub-section 2.2 – Quality Aspects; Sub-sub-section 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects: page 16;
*"Overall, information on manufacture and control of the active substance, finished product **and novel excipient (rHuPH20)** has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics. A list of recommended measures will ensure an adequate maintenance of the quality of the product"*

(vii) Section 2 – Scientific discussion; Sub-section 2.3 – *Non-clinical aspects*; Sub-sub-section 2.3.3. Pharmacokinetics: page 25: –
"Pharmacokinetics of trastuzumab (RO0452317) after SC administration of trastuzumab/rHuPH20 to Cynomolgus monkey
***Trastuzumab was administered** SC at a dose level of 25 mg/kg **in a formulation containing recombinant human hyaluronidase (rHuPH20) as excipient** (6000 U rHuPH20/mL formulation). The …."*

(viii) Section 2 – Scientific discussion; Sub-section 2.3 – Non-clinical aspects; Sub-sub-section 2.3.7. Conclusion on the non-clinical aspects; Page 31: -
*"Extensive data of non-clinical pharmacology in vitro and in vivo after IV administration available through the long experience with Herceptin are supplemented by a single dose local tolerance study in rabbits and a 13-week repeat dose toxicity study in Cynomolgus monkeys **performed to confirm that the change in route of administration and the use of the novel excipient recombinant human hyaluronidase (rHuPH20) did not have an effect on the Herceptin safety characteristics.** Herceptin subcutaneous formulation was locally and systemically well tolerated."*

(ix) Section 3 – Benefit-Risk Balance: Benefits: Beneficial effects: Page 31: -
*"The present application provides data to support the license extension of the trastuzumab SC (vial) formulation (Herceptin SC) as a fixed dose (600 mg) for three-weekly assisted administration via a handheld syringe. **The SC administration of trastuzumab is enabled by the use of recombinant human hyaluronidase (rHuPH20), a key excipient in the trastuzumab SC formulation which acts as a permeation enhancer.** This application is based on data from one phase I pharmacokinetic (PK) dose-finding and dose-confirmation study (BP22023) and one pivotal, phase III clinical study (BO22227) in patients with EBC in the neoadjuvant-adjuvant setting"*

The MABTHERA Marketing Authorisation

86 A similar situation has also occurred with the MabThera MA provided in support of SPC/GB16/039.

87 The MA for MabThera was originally granted following Commission Implementing Decision C(1998) 1464 for two different pharmaceutical forms of MabThera, 100 mg concentrate for solution for infusion, authorised as EU/1/98/067/001; and 500 mg concentrate for solution for infusion, authorised as EU/1/98/067/002 (see Table 1). The human recombinant hyaluronidase is not present in either of the two original physical forms of MabThera but is in the third physical form of MabThera, authorised as EU/1/98/067/003, which is a 1400 mg solution for subcutaneous injection. Thus the human recombinant hyaluronidase is only relevant for the physical form that is used for subcutaneous injection.

88 Commission Implementing Decision C(2014) 2048 of 21 March 2014 approved the changes to the marketing authorisation, originally approved by Commission Implementing Decision C(1998) 1464 and adds all the additional information relevant to this extension to a new physical form and strength of MabThera. As indicated in the updated SmPC, and as confirmed by the EPAR (which includes the assessment report from the CHMP on the application for this line extension), this new physical form is approved for use in some of the same treatments as the original physical form, i.e., Non-Hodgkin's lymphoma (NHL).

89 This updated MA is the one cited in support of SPC application SPC/GB16/039 for the combination of rituximab and hyaluronidase.

90 The updated SmPC for MabThera discusses the role of hyaluronidase in an almost identical manner to that for Herceptin (see above) so I will not repeat what are essentially the same details here.

91 Similarly, the EPAR for MabThera (which includes the assessment report from the CHMP on the application for the line extension)[34] discusses the role of hyaluronidase in an almost identical manner to that for Herceptin (see above) so I also will not repeat what are essentially the same details here.

92 However, I do note that the EPAR for MabThera provides some further detail about hyaluronidase and how it works (see Section 2 – Scientific discussion; Sub-section 2.2 – Quality Aspects; Sub-sub-section 2.2.3. Finished Medicinal Product - Pharmaceutical Development; pages 12-13; my emphasis added in bold):

> *"The **development of this subcutaneous formulation uses a new technology based on an excipient, recombinant human hyaluronidase (rHuPH20), which acts as permeation enhancer, allowing larger volumes to be comfortably administered via the SC route**. While the intravenous infusions typically require 2-4 hours, the subcutaneous formulation injections into the abdominal region will take approximately 5 to 7 minutes to administer. **Recombinant rHuPH20 is considered a novel excipient** (conform to a recent*

[34] *Identified as procedure number EMEA/H/C/000165/X/0083.*

trastuzumab application) and the applicant has also provided a full dossier with details of manufacture, characterisation and control, accordingly."

93 This EPAR also makes a cross-reference to that for Herceptin (see Section 2 – Scientific discussion; Sub-section 2.2 – Quality Aspects; Sub-sub-section 2.2.1 – Introduction; page 11; my emphasis added in bold), stating:

> *"A new MabThera dosage form for subcutaneous injection has been developed (referred to as MabThera SC) and Roche is seeking approval for it with this Extension Application.* ***The new SC formulation contains rHuPH20, a recombinant human hyaluronidase which enables the subcutaneous injection of large volumes and acts as a permeation enhancer****.*
> *…….*
>
> *Hyaluronidase (rhuPH20) is produced in CHO cells.* ***rhuPH20 is a novel excipient*** *and detailed information on the manufacture and control is presented in the dossier. However,* ***rhuPH20 has been recently reviewed, as a novel excipient in the following procedure; Trastuzumab SC, EMEA/H/C/278/X/60****. Trastuzumab SC is also marketed by Roche Registration Ltd. Manufacture and the manufacturing process for rhuPH20 at Avid is similar to the material to be used in Trastuzumab SC and MabThera SC. The Trastuzumab SC procedure received a CD in 2013."*

What is the role of hyaluronidase based on the respective marketing authorisations?

94 Having considered the information that is available from both MAs, there is nothing therein to suggest that the hyaluronidase should be considered as an active ingredient. It is clearly identified as an excipient and its role is identified as making it easier to administer Herceptin or MabThera subcutaneously.

95 This is, in effect, the argument presented by the examiner in each case and, on the face of it, this argument has considerable force in relation to each application at issue in the case.

96 This analysis of what is provided by the MAs themselves is entirely consistent with the approach endorsed by the UK courts in *Yeda*[35] and, subsequently, in *Newron*[36]. It was confirmed that, in analysing what is the active ingredient, the correct approach is

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[35] *See Yeda, footnote 8 – see especially para 26.*

[36] *See Newron, footnote 7 – see especially paras 33 and 41. The earlier Newron decision from the Patents Court referred to was itself an appeal from IPO decision BL O/1053/22 concerning Newron's SPC application (see also footnote 31). This decision of the Patents Court has itself also been subject to a further appeal to the Court of Appeal. In a decision dated 15 February 2023, the Court of Appeal dismissed the appeal (see Newron Pharmaceuticals SPA v The Comptroller General of Patents, Trademarks And Designs [2024] EWCA Civ 128 (15 February 2024) (bailii.org). The points made in para 33 and 41 still stand.*

to consider this in a strict manner and examine what the active ingredient is and not what it does.

97 I think that there is a further argument in support of the conclusion reached by the examiner that is entirely consistent with approach endorsed by the UK courts in *Yeda* and in *Newron.*

98 Article 1 of Commission Implementing Decision C(2000) 2539 details the active ingredient as "*Herceptin – Trastuzumab*"[37]. Article 1 of Commission Implementing Decision C(2013) 5603 does not make any statement about changes being necessary to the active ingredient and/or to the medicinal product. However, it does state that Annex I of C(2000) 2539 is amended and replaced by the text of Annex I of C(2013) 5603. An examination of Annex I of C(2013) 5603 indicates that it contains the text of the SmPC for EU/1/00/145/001 (Herceptin IV) as well as that for the line extension EU/1/00/145/002 (Herceptin SC). Annex I of C(2000) 2539 which it replaces contains the SmPC for EU/1/00/145/001 only (Herceptin IV). I think that this further supports the conclusion that the medicinal product and the active ingredients are the same in both cases. These two implementing decisions relate to the same medicinal product Herceptin that comprises the same active ingredient, trastuzumab. There is nothing to suggest that the active ingredients in Herceptin change from trastuzumab in EU/1/00/145/001 to trastuzumab and hyaluronidase in EU/1/00/145/002 which is the consequence of the approach being suggested by the applicant in the present case. If this was the case surely the new Annex I could not include the SmPC for EU/1/00/145/001 as well as that for EU/1/00/145/002 unless they both relates to the same medicinal product and active ingredient?

99 I find further support for this approach of considering what is the active ingredient in the medicinal product identified by the Commission decision and the SmPC in recent IPO decisions mentioned below[38-40].

100 Based on the information provided in Commission Implementing Decision C(2013) 5603, I do not believe that the EMA considered recombinant human hyaluronidase to be an active ingredient and thus, while clinical trials were conducted which involved hyaluronidase, as discussed below, these trials were conducted to show how the new component in Herceptin SC (EU/1/00/145/002) interacted with the trastuzumab and how it compared to the Herceptin IV form (EU/1/00/145/001) in achieving the same therapeutic outcome – the treatment for HER2 breast cancer.

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[37] *Article 1 of C(2000) 2539 states as follows (my emphasis added in bold):*

> *"The marketing authorisation referred to in Article 3 of Regulation (EEC) No 2309/93 is hereby granted in respect of the medicinal product: "**Herceptin – trastuzumab**" whose characteristics are summarized in **Annex I** hereto. This medicinal product shall be entered in the Community Register of Medicinal products under the number:*
>
> ***EU/1/00/145/001** Herceptin- Trastuzumab – 150 mg – Powder for concentrate for solution for infusion – intravenous use – 1 vial (glass)"*

Is analysing the marketing authorisation the whole story?

101 However, the applicant argues that referring to the MA in this way is too literal or simplistic an approach; that it ignores the fact that hyaluronidase has properties that mean it should be considered as an active ingredient; and that the above approach is not in line with that taken (by this hearing officer) in the recent IPO *Ethicon*[38] decision which took into account all the materials available.

102 I will examine the arguments made by the applicant in detail below.

103 As this hearing officer has done in a number of recent office decisions, I am indeed prepared to take a step back and consider all the materials provided by the applicant, when considering what is the active ingredient in question. However, when doing so, I have always been looking to find out what is the active ingredient in the medicinal product that is identified in the marketing authorisation. Identification of the active substance in the medicinal product is made by the body responsible for approving medicinal products for human use under the Medicines Directive - as is clearly identified in Article 3(b) of the regulation. In the present case, the relevant responsible body was the European Medicines Agency (EMA)[1]. The EPAR is prepared by the EMA as part of the approval process. The inclusion of the EPAR to supplement the information in the Commission's Implementing Decision and the related SmPC is thus helpful in determining what is the active ingredient. Taking account of the EPAR in this way as part of the process to determine what is the active ingredient was accepted by the court in *Abraxis UK* (see paragraph 59 therein).

104 This reflects the overall approach that was followed, not just in the *Ethicon* decision referred to by the applicant but also in the recent *Roche Glyart*[39] and *Newron* decisions[40] from the IPO. In each case, analysis of what was the authorised active ingredient was necessary and this analysis has to be led by what is disclosed in the Commission Implementing Decision, the SmPC and the EPAR before taking into account, if any, further materials. It may be that no further materials are necessary to consider after these documents have been considered. Hence the characterisation of this approach as being one that is "SmPC/EPAR-led" .

105 I have considered the Commission Implementing Decision, the SmPC and the EPAR in the previous section as this is the starting point for identifying what is the active ingredient disclosed in the MA. In any further consideration of additional materials, any comments in relation to the role of hyaluronidase as an active ingredient will not

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[38] See IPO decision BL O/136/22, Ethicon, Inc., and Omrix Biopharmaceuticals, Inc., relating to application SPC/GB14/029 at Patent decision O/242/22 (ipo.gov.uk), especially paras 60-84.

[39] See IPO decision BL O/711/22, Roche Glycart AG., relating to application SPC/GB17/055 at Patent Decision O/711/22 (ipo.gov.uk).

[40] See IPO decision BL O/1053/23, Newron Pharmaceuticals, SpA., relating to application SPC/GB15/046 at Patent Decision O/1053/22 (ipo.gov.uk). This decision is also discussed in footnotes 31 and 36 above.

be considered in isolation, they will be considered as a whole alongside the points made in the Commission Implementing Decision, the SmPC and the EPAR.

106 With this overall approach in mind, I will consider two questions:

> (a) *does human recombinant hyaluronidase have properties that mean it should be considered as an active ingredient?*
>
> *(b) is the metabolic effect of human hyaluronidase (rhuph20) discussed in the marketing authorisation?*

Does human recombinant hyaluronidase have properties that means it should be considered as an active ingredient?

107 In their skeleton argument (see para 31), filed in advance of the hearing, the applicant, referring to the CJEU decisions in *MIT, GSK, Forsgren, Bayer* and *Abraxis* (see above), stated that this caselaw establishes two conditions which must be met to define an active ingredient:

- Firstly, the ingredient in question has an effect on the human body i.e. a metabolic effect.
- Secondly, that the presence and effect of the ingredient is reflected in the technical information submitted as part of the MA and contributed to the delay in obtaining authorisation, i.e. covered by the therapeutic indication of the MA.

The applicant then goes on to say, taken together, these two conditions indicate "*In other words, that it* [the active ingredient] *has a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indications of the marketing authorisation*".

108 The applicant considers that the first condition for hyaluronidase to act as an active ingredient is met because of "*the basic science underlying its use*" as explained in the '643 patent filed in support of this SPC application and in some of the references identified in that patent. Mr Mitcheson argued that hyaluronidase has been shown to have both general and specific effects regarding the treatment of cancer and that its "*presence leads to a significant advance in the treatment of cancer*". The general effects were those referred to in the literature such as the papers cited in the patent which show that "*hyaluronidase has been shown to inhibit tumour growth*" and that it has a metabolic effect of its own i.e. *"It has specific enzymatic activity which modifies the structure, and thus the function, of the subcutaneous extracellular matrix*".

109 In support of this argument, Mr Mitcheson asked me to consider the basic patent '643 and several other documents, including a number of journal references, cited in the basic patent which, the applicant believes, supports their argument that recombinant human hyaluronidase has an effect, be it pharmacological, immunological or metabolic, on cancer. He directed me to several paragraphs in basic patent '643 which, he asserted, provided evidence of an effect of recombinant human hyaluronidase in cancer, including:

(i) paragraphs [0046] and [0049] show that recombinant human hyaluronidase has a metabolic effect on the body (my emphasis added):

> *[0046] Methods for the use of sHASEGP's in the removal of glycosaminoglycans are also provided.* ***sHASEGP's open channels in the interstitial space through degradation of glycosaminoglycans that permit the diffusion of molecules*** *less than 500nm in size. These channels remain for a period of 24-48 hours depending on dose and formulation. Such channels can be used to facilitate the diffusion of exogenously added molecules such as fluids, small molecules, proteins, nucleic acids and gene therapy vectors and other molecules less than 500nm in size.*
>
> *……*
>
> *[0049] In other indications, a single short acting dose is preferable.* ***Temporary removal of glycosaminoglycans can be used to enhance the delivery of solutions and drugs into interstitial spaces****. This can be very useful for the diffusion of anesthesia and for the administration of therapeutic fluids, molecules and proteins.* ***Subcutaneous*** *and intramuscular* ***administration of molecules in the presence of sHASEGP's also facilitate their systemic distribution more rapidly****. Such methods are very useful when intravenous access is not available or where more rapid systemic delivery of molecules is needed. Delivery of other large molecules such as Factor VIII, that are poorly bioavailable upon subcutaneous administration, made be injected with sHASEGP's to increase their availability.*

(ii) paragraph [0047] discloses a number of possible uses and effects of glycosaminoglycans (GAG, such as hyaluronidase) as follows:

> *"[0047] sHASEGPs can also be used to remove excess glycosaminoglycans such as those that occur following ischemia, reperfusion, inflammation, arteriosclerosis, edema, cancer, spinal cord injury and other forms of scarring. In some instances, sHASEGP's can be delivered systemically by intravenous infusion. This can be helpful when local access is not readily available such as at the heart or brain or in the case of disseminated neoplasm wherein the disease is through the body. Super-Sialated sHASEGP's are preferable to increase serum half-life and distribution over native hyaluronidase enzymes that lack terminal sialic acids".*
>
> Mr Mitcheson further pointed out, in this regard, that *"There is a direct action where the molecules of the invention can be used to remove the GAGs that are made during diseases such as cancer"*;

(iii) paragraph [281] and [283] which indicate that sHASEGP polypeptides "*can be formulated as pharmaceutical compositions*" and that these "*polypeptides can be formulated as the sole pharmaceutically active ingredient in the composition or can be combined with other active ingredients*".

(iv) paragraph [0361] and the scientific journal articles referenced therein, particularly *Baumgartner et al.*[41], Counsel highlighted a passage from the introduction of *Baumgartner et al.* (reproduced below, my emphasis in bold):

> *"There is much evidence indicating that alterations in the extracellular matrix composition of tumour stroma can arise as a result of altered synthesis by host cells in response to tumour cell influences, inducing resistance to a variety of drugs.*
>
> ***Therefore, the concept of cancer therapy by means of (bio)chemical modification of tumour cells or normal tissue and extracellular matrix such that a therapeutic gain can be achieved using conventional therapeutic modalities is a promising one**.*
>
> *We report here on a phase I study of the improvement in therapeutic efficacy in loco-regional treatment of chemo-resistant malignant diseases achieved by adding hyaluronidase to the appropriate chemotherapy protocol."*

He then went on to argue that *"there can be no doubt that the hyaluronidase is an active ingredient in the sense required by law because it is achieving biochemical modification of the tumour cell. It is an enzyme, so it is dissolving or, in chemical reaction, the molecules around the tumour cells, and that is improving the ability of the other ingredient to overcome the resistance which has occurred"*.

(v) paragraph [0362] where Mr Mitcheson directed me to the statement in this paragraph that *"In addition to its indirect anticancer effects, cattle derived hyaluronidase has direct anticarcinogenic effects. Hyaluronidase prevents growth of tumours transplanted into mice"*. He also took me to the paper by *De Maeyer et al*. referenced therein[42] which concerned a study examining two mouse strains, C57BL/6 and HW23, which have different levels of circulating hyaluronidase, and investigated the effects of these hyaluronidase levels on resistance to tumour development. This study appears to indicate that higher levels of circulating hyaluronidase increase resistance to tumour development in lung carcinoma and melanoma.

(vi) paragraph [0372] and the 1998 *St. Croix et al.* paper referenced therein[43]. This paper discusses the use of bovine testicular hyaluronidase to treat intact multicellular spheroids of a mouse mammary tumour EMT-6 by disaggregating and dispersing the spheroids making them more susceptible to the effects of chemotherapeutics. The hyaluronidase in this case was administered intraperitoneally.

(vii) Mention is also made in paragraphs [0373] and [0374] that "*sHASEGP can be used as a chemotherapeutic agent (alone or in combination with other chemotherapeutics) in the treatment of any of a variety of cancers, particularly invasive tumours. For example, sHASEGP can be used in the treatment of small*

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[41] *Baumgartner et al., 1988, Reg. Cancer Treat.; 1: pp 55-58*

[42] *De Maeyer et al.,1992, Int. J. Cancer, 51: pp 657-660*

[43] *St Croix et al., Cancer Lett., 1998, Sep 11; 131(1): pp 35-44*

lung cell carcinoma ……" and that the sHASEGP can also be used to increase the sensitivity of tumours that are resistant to conventional chemotherapy.

(viii) In addition to the paragraphs identified above, Mr Mitcheson also took me to paras [0001]-[0003], [0007], [0008], [0359] and [0363] which illustrate that there is a need for hyaluronidase of human origin that can be used in chemotherapy as a therapeutic agent itself or in conjunction with other chemotherapeutic agents.

110 In relation to the second condition, the applicant makes reference to the specific effect of hyaluronidase (see para 41 of skeleton argument), citing clinical trial BO2222Y from the MA, as follows:

> "*As for the specific effect in combination with trastuzumab, this is demonstrated by the clinical trial BO22227 reported at p.50 of the Herceptin SmPC/EPAR (cf the Forsgren case). Whilst 40.7% of patients in the control group receiving trastuzumab alone (intravenously) lacked cancer cells in the breast, some 45.5% of patients receiving trastuzumab and hyaluronidase achieved the same status, an improvement rate of over 10%. This is an important advance given the seriousness of the disease in question."*

111 In the above-mentioned clinical study, the effect of hyaluronidase on the pharmacokinetics of trastuzumab in the subcutaneous formulation (Herceptin SC) was compared to that of trastuzumab in the intravenous formulation (Herceptin IV, see SmPC, Section 5.2: Pharmacokinetic properties, page 51). As a consequence, the legal test outlined by the applicant (see above) is fulfilled in their view. The applicant argued that this shows, not only that the hyaluronidase is having an effect on the human body, but it is doing so in a way that is consistent with the granted marketing authorisation. As such, hyaluronidase can be considered to have all the features of an active ingredient – it has a metabolic effect, it is part of the clinical testing that contributed to the delay in obtaining authorisation and according to the applicant, citing the CJEU decision in *Bayer*, the hyaluronidase "*is at least as active as the safener in Bayer*".

112 I do not agree with this characterisation by the applicant of the conditions to be met to determine if a substance is an active ingredient. I do not consider that the first condition proposed by the applicant is correct – it is not a question of whether the substance is an active substance because it has a metabolic effect on the body. This is too general. I believe that the case law is clear in that the condition to be met is more specific, i.e., does the substance in question have a pharmacological, immunological or metabolic action of its own **which is covered by the therapeutic indications of the marketing authorisation** (as the CJEU concluded in *Forsgren,* my emphasis added in bold).

113 Such references as those referred to by Mr Mitcheson and described above from the '643 patent and the related documents cited therein fall short in my view of showing that something is acting as an active agent for a particular disease. This is especially true when set alongside the fact that the MA indicates it is acting as an excipient. I consider that while these references indicate that hyaluronidase has properties that show it has potential to be used to treat cancer in general and that it is worth investigating further, it does not provide information on how hyaluronidase acts in the

treatment of the specific cancers of interest, e.g., HER2 breast cancer or NHL, the specific treatments referred to by the respective MAs.

114 In his argument that this "*metabolic effect*" supports hyaluronidase as an active ingredient, Mr Mitcheson suggests that rHuPH20 is having an indirect effect on breast cancer, by allowing diffusion of trastuzumab into the body, and pointed to the decision of *Bayer*, to support his position. However, I do not think that this takes sufficiently into account the decision in *Forsgren,* which confirms that the active ingredient must have an effect of its own in the relevant therapeutic indication. In my view, it is clear from the MA that the therapeutic effect that has to be taken into account for Herceptin is not cancer in general but is the rather more specific HER2 breast cancer. The latter is the therapeutic indication that has been approved by the MA for Herceptin, not the former. Similarly, for MabThera, the indication is for NHL rather than cancer in general.

115 While I appreciate Mr Mitcheson' s eloquence in presenting the applicant's case in the best light he can, I do not think that I can stretch or redefine the meaning of excipient so that it covers active ingredient in the way that the applicant is inviting me to do so.

116 I note that the '015 patent has similar disclosure and cites the same literature references as the '643 patent. Therefore, the above points also apply to SPC application SPC/GB16/039, with the additional point that, so-far as I have been able to establish, neither the '015 patent, nor the literature documents cited therein, contain any evidence demonstrating the effect of recombinant human hyaluronidase in non-Hodgkin's lymphoma (NHL).

Is the metabolic effect of human hyaluronidase (rHuPH20) discussed in the marketing authorisation?

117 In my view the "*metabolic effect*" identified by Mr Mitcheson is what is being referred to and acknowledged in the SmPC and EPAR of the respective marketing authorisations filed in the support of the present SPC applications; see, for example (and as already mentioned above):

(i) Herceptin SmPC
- Section 5.1, Pharmacodynamics properties; p 41 (2nd para).
- Section 5.3, Preclinical safety data - Subcutaneous formulation: p 52.
- Section 6.1, List of Excipients; p 52.

(ii) Herceptin EPAR, Section 2 – Scientific discussion:
- Sub-section 2.1 – Introduction; p10
- Sub-section 2.2 – Quality Aspects,
  - Sub-sub-section 2.2.1, Introduction: p10
  - Sub-sub-section 2.2.3, Novel Excipient (rHuPH20): p 13
- Sub-section 2.3 – Non-clinical aspects,
  - Sub-sub-section 2.3.1, Introduction: p16

This is in contrast to what, for example, the SMPC and the EPAR identified as the active substance; see, especially:

(iii) Herceptin SmPC
- Section 2: Qualitative and Quantitative Composition, p29
- Section 5.1, Pharmacodynamics properties; p 41 (3rd para)

(iv) Herceptin EPAR, Section 2 – Scientific discussion:
- Sub-section 2.2 – Quality Aspects,
  - Sub-sub-section 2.2.2, Active Substance: p10

118 Indeed, this would appear to be the key role of hyaluronidase in the subcutaneous formulation and, in contrast to the view of the applicant, relates, in my view, to its action as an excipient – i.e., it facilitates the delivery of the active ingredient trastuzumab to where it can exert its therapeutic impact. Thus, I consider that this is explained in the context of hyaluronidase acting as an excipient, i.e. facilitating the delivery of the active ingredient trastuzumab. I do not consider that this is an example of hyaluronidase acting as an active ingredient in its own right as the applicant has suggested. Also, I think this is consistent with the role of hyaluronidase identified in the patent – see paragraph 47 quote above – the removal of GAGs.

119 Furthermore, the patent acknowledges that the hyaluronidase can be, and is, used in combination with other therapeutic agents: see, for example paras [0283], [0363], [0374] referred to above from the '643 patent; see also paragraph [0052] and [0360] from this patent which gives example of the use of hyaluronidase in combination with an anaesthetic. It also indicates in [0361] (see above) that *"hyaluronidases have also been used as a "spreading agent" to enhance the activity of chemotherapeutics and/or the accessibility of tumours to chemotherapeutics".* This suggests to me the information in the patent can just as easily be read as supporting the action – penetration of GAGs - which the SmPC and EPAR identify as that of the excipient but which the applicant and Mr Mitcheson are asking me to identify as indicative of an active ingredient.

120 The MA identifies hyaluronidase (rHuPH20) as an excipient. The testing carried out that involved hyaluronidase was in my view entirely consistent with its role as an excipient. It was carried out to answer the question of whether Herceptin SC is at least as effective as Herceptin IV – see SmPC, p50 (section 5.1: Pharmacodynamic Properties: Subcutaneous Formulation) which indicates that:

> "*Study BO22227 was conducted to demonstrate non-inferiority of Herceptin subcutaneous formulation versus Herceptin intravenous formulation based on co-primary PK and efficacy endpoints*.".

It is already known that Herceptin IV, which includes trastuzumab but not hyaluronidase, works and when the new physical form (Herceptin SC) is investigated it is found to be at least as good, if not better (relative to the older form). It appears to me that the reason why Herceptin SC appears to work better than Herceptin IV, is because the hyaluronidase makes it easier for the active ingredient to move through the GAG layer when the trastuzumab is delivered subcutaneously.

121 I do not consider that the two conditions, identified by the applicant, can be combined, as the applicant says to meet the requirement that: "(*in other words that) it has a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indications of the marketing authorisation*." I do not consider that the latter is the consequence of the two conditions identified by the applicant. As I

acknowledged in my *Ethicon* IPO decision[29], and in line with *Forsgren*, I think it is possible for evidence from other sources to be used to supplement or offer additional material to that disclosed in the marketing authorisation. However, if there is nothing on the issue in the marketing authorisation, I do not consider that evidence from other sources can be used to establish that one component in a medicinal product can be considered as an active ingredient when it has been identified as an excipient. I am satisfied that evidence from other materials can be considered to supplement the information provided in the marketing authorisation including the SmPC and its related EPAR but not, to in effect, provide information for which there is no basis in the SmPC or EPAR

122 The applicant argued that the CJEU judgment in *Bayer* provides a basis on which the additional properties of hyaluronidase that the applicant has identified in the patent and the references cited therein may be taken into account. They indicate that the hyaluronidase "*is at least as active as the safener in Bayer*". I am not persuaded by this analogy.

123 First of all, as already outlined above, the identification of the active ingredient and the other elements in the medicinal product is a matter for the regulatory authority (in this case the EMA). This decision is based on the assessment carried out by the regulatory authority working with the applicant for the MA and the clinical evidence they have provided. While deciding whether an SPC can be granted or not, is a matter for the IPO, I do not think that it is correct to ignore or, at least, downplay the information in the MA and take greater account of the information in the patent as I believe is the consequence of following the approach proposed by the applicant.

124 Secondly, medicinal products for human (or animals), such as Herceptin or MabThera, do not contain safeners. These are a particular type of component in plant protection products. They are defined within the system for granting market approval for the active ingredients used and for applying the commercial plant protection products comprising these active ingredients – see Directive 91/414/EC[44]. As the judgement in *Bayer* stated, whether a safener in a plant protection product has an impact on the grant of an SPC for a plant protection product only falls to be considered if it is shown that in the assessment of the active ingredient itself, the safener has also been part of this assessment and the related delay for the regulatory approval process that the SPC system is designed to address. The formulation and approval process of plant protection products is not the same as that for medicinal products (human and/or veterinary) and so the proposed read across by the applicant is not valid in my view.

125 Thirdly, I consider that in the present case, the assessment of the active ingredient trastuzumab or rituximab has already taken place (see Table 1) without the presence of hyaluronidase for both Herceptin and MabThera and, for both, it has been shown to have the necessary therapeutic activity in its absence and its presence – thus reinforcing the view that it is contributing to these formulations in a way different to that expected for an active ingredient. The assessment of hyaluronidase only takes place in some of the formulations and, as outlined above, was in the context of how it helped the trastuzumab (or the rituximab) to achieve its therapeutic activity.

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[44] now superseded by Regulation 1107/1991 (see also footnote 30 above).

126 Fourthly, while I note that recital 17 of the PPP SPC regulation indicates that certain recitals and articles from this regulation are valid for the interpretation of certain recitals and articles of the Medicines SPC regulation, Article 1 and the definition of active ingredient is not covered by this.

What is the role of the marketing authorisation in identifying the different components of the medicinal product?

127 Following on from the points discussed in the previous section, I consider, firstly, that the starting point for identifying the active ingredient and the other components in the medicinal product is the marketing authorisation and not the patent. When considering if an SPC application meets the requirement of Article 3(d) it is correct to start this consideration with the authorisation and what it covers. Just because the patent may include additional information about the hyaluronidase does not in my view mean that you can ignore or not place suitable weight on the role that the hyaluronidase plays in the medicinal product as explained in the MA. In this instance, the MA refers to the hyaluronidase as an excipient, making the delivery of the active ingredient trastuzumab (or rituximab) possible by the subcutaneous route. It seems logical that the hyaluronidase is only necessary for subcutaneous administration of trastuzumab because there are GAGs present in the application site.

128 The MA discloses what specific conditions are being treated in humans (or animals). It discusses the medicinal product, with the active ingredient in it, explains what the benefits and the risks are of using this medicinal product with the listed active ingredient (or ingredients) and other excipients. The MA also explains how this product should be stored and administered and whether the latter can be achieved by the patient themselves, or if a medical practitioner, such as a nurse or doctor, is needed. When the formulation of a medicinal product is changed, then the new formulation including all its elements have to be assessed – this includes the excipients as well as the active ingredient(s).

129 In the present case, the hyaluronidase is involved in a study (with the relevant active ingredient) to confirm that it does not reduce the impact of the medicinal product when it is used in a different way and that it facilitates delivery of the active ingredient trastuzumab through the skin. However, this does not mean that this is enough to establish that it is displaying the properties consistent with the definition of an active ingredient.

130 I consider that this analysis is entirely consistent with the case law which indicates that active ingredient has to be interpreted narrowly (see *MIT, Yissum, Forsgren* and *Abraxis UK*) and must have the specific activity covered by the marketing authorisation.

131 For an SPC to be granted for a combination of A and B, I consider that it is necessary for the substances in question to be identified in the marketing authorisation as having a pharmacological, immunological or metabolic action which is covered by the therapeutic indications of the marketing authorisation. I do not think, for example, that a reference to the literature cited in the patent filed in support of this SPC application

that indicates that hyaluronidase has been shown to reduce tumour size in a number of animal studies involving different types of tumour is more significant than the fact that the MA itself refers to hyaluronidase as an excipient and explicitly refers, for example, to its role in facilitating subcutaneous delivery of trastuzumab for use in the treatment of HER2 Breast Cancer. I could equally note in this regard that the studies identified by the applicant involve a variety of different types of tumour and although breast cancer is identified as one possibility, NHL is not. Also, the hyaluronidase is usually applied directly to the tumour of interest rather than remotely from it as discussed in the MA.

132 The SPC system sits at the border of the regulatory system - that determines what can be safely used as a medicine – as exemplified by the MA - and the patent system – that determines what pharmaceutically active products are protected by a patent but cannot be exploited until the regulatory approval is completed – and so merit some additional protection to make up for this loss of exclusivity. In considering a question about what active ingredients are present in the medicinal product that has been authorised for use in humans, I cannot see how it is that I should place more importance on a general disclosure in the patent than on a lack of disclosure in the marketing authorisation or an indication in the MA that the hyaluronidase is acting as an excipient. As was the case in the recent IPO *Ethicon* decision[26], I accept that I cannot rule out that there may be other interactions that involve hyaluronidase that may occur at the same time, but, for the purpose of deciding if an SPC can be granted, in this case, the most important consideration is what role do the SmPC and the EPAR identify is being played by hyaluronidase.

133 Nothing in the SmPC or the EPAR suggests, in my view, that the hyaluronidase is acting in any fashion other than as an excipient, i.e., it is breaking down GAGs at the injection site and making it easier for trastuzumab to penetrate into the blood stream and so exert its therapeutic effect on HER2 breast cancer cells. It is only the latter role that has been identified and assessed for the purpose of the extension to the MA for Herceptin (and also for the purpose of the extension to the MA for MabThera). Any other contribution made by the hyaluronidase, unless it is specifically accounted for and referred to in the marketing authorisation is, in my view, not relevant for the purposes of deciding the grant of an SPC.

134 Determining whether an SPC can be granted is an autonomous decision made under the relevant SPC regulation by the relevant competent authority, in this case the UK-IPO. If I was to place the emphasis on the additional information referred to by the applicant that I am being invited to, I think that the logical consequence of this is that I would be ignoring or contradicting the process that is used to approve the Marketing Authorisation. I think that if there is not a clear direction in the marketing authorisation, (which I take to include the Commission Implementing Decision, the SmPC and/or EPAR) that a component of a medicinal product is an active ingredient, then I do not believe that further material such as the basic patent or references cited therein can overcome this.

Role of Hyaluronidase - excipient or active?

135 Having considered the Medicines SPC Regulation and the relevant case law, I conclude that, in order for a substance to be considered an active ingredient, it is necessary that the marketing authorisation, including the EPAR, must contain, at the very least, some indication that the substance gives rise to a pharmacological, immunological or metabolic effect of its own for the therapeutic indication covered by the MA. Therefore, in the case of SPC application SPC/GB15/047, it must be apparent from the marketing authorisation for Herceptin that human recombinant hyaluronidase has a pharmacological, immunological or metabolic effect of its own in HER2 breast cancer, and in the case of SPC/GB16/039, it must be apparent from the marketing authorisation for MabThera that human recombinant, hyaluronidase has a pharmacological, immunological or metabolic effect of its own on non-Hodgkin's lymphoma (NHL), in order for it to be considered an active ingredient within the meaning of Article 1(b). I can find no such indication in the either MA and, in the absence of any such indication, I do not believe that it is possible to rely upon evidence outside of the marketing authorisation, in order to show that this is the case.

Relevance of decisions from other jurisdictions

136 At the hearing Mr Mitcheson drew my attention to parallel SPC applications that have been litigated in other jurisdictions around Europe, including Spain, Portugal, and Poland, where following related appeals the SPCs have been granted, and France and Germany where SPCs have been refused (albeit still subject to appeal in Germany). The applicant provided the original language decision and a verified English translation in each example.

137 Having reviewed these, I note that in at least one case (Germany) the conclusion reached by the relevant competent authority for granting SPCs was the same as that outlined above, i.e., based on the marketing authorisation for Herceptin and, in contrast to trastuzumab, human recombinant hyaluronidase does not have a pharmacological, immunological or metabolic effect of its own in HER2 breast cancer.

138 At the time of the hearing in the UK, the decision to reject the SPC application in Germany was under appeal. I note that the appeal court in France, the Cour de Cassation, also came to a similar conclusion (on appeal from the decision of the French IPO (INPI)) to reject the corresponding SPC.

139 However, I do also acknowledge that a number of other national jurisdictions have decided to grant this SPC on appeal from the original decisions of the respective competent authorities to reject the application, for example Spain and Portugal.

140 I would like to thank the applicant for providing the copies of the decisions from other jurisdictions and their respective translations into English. For the purposes of the present decision, these decisions from other national jurisdictions, while interesting, are not binding on me. I need to look afresh at this these two cases and determine whether the examiners are correct in their view that the respective SPC applications do not meet the requirements of the Medicines SPC Regulation. This requires me to consider afresh the relevant law, caselaw, the written arguments put forward by the

examiner and the written and oral submissions from the applicant and their representatives. The decision above sets out my analysis and why I have come to the conclusions summarised below. Please see my conclusions below

Conclusions

SPC/GB15/047 - "Trastuzumab and recombinant human hyaluronidase"

141 Taking all of the above into account, I consider that the marketing authorisation EU/1/00/1454/002 for the medicinal product Herceptin, cited in support of SPC application SPC/GB15/047 for the product "*Trastuzumab and recombinant human hyaluronidase*", is not the first authorisation to place this product on the market in the UK as a medicinal product and so does not meet the requirements of Article 3(d) of the Medicines SPC regulation..

142 I consider that the Commission Implementing Decision, the SmPC, and the EPAR for the medicinal product Herceptin identify recombinant human hyaluronidase as an excipient only.

143 The Commission Implementing Decision, the SmPC, and the EPAR for the medicinal product Herceptin do not show that recombinant human hyaluronidase has a metabolic, pharmacological, or immunological effect with respect to HER2 breast cancer, the therapeutic indication covered by this marketing authorisation. As such, recombinant human hyaluronidase cannot be considered to be an active ingredient under Article 1(b) of the SPC regulation.

144 As a consequence, SPC application SPC/GB15/047 cannot be considered as an application for a combination of two active ingredients, i.e., trastuzumab and recombinant human hyaluronidase. Rather, it has to be considered as an application for a single active ingredient (trastuzumab).

145 This SPC application also does not comply with Article 3(c) of the Medicines SPC Regulation given the existence of an earlier granted SPC for trastuzumab.

146 SPC Application SPC/GB15/047 application is thus rejected under Article 10(2) of the Medicines SPC Regulation for failure to meet the conditions laid down in the Regulation.

SPC/GB16/039 - "Rituximab and recombinant human hyaluronidase"

147 Taking all of the above into account, I consider that the marketing authorisation EU/1/98/067/003 for the medicinal product MabThera cited in support of SPC application SPC/GB16/039 for the product "*Rituximab and recombinant human hyaluronidase*" does not meet the requirements of Article 3(d) of the SPC regulation.

148 I consider that the Commission Implementing Decision, the SmPC, and the EPAR for the medicinal product MabThera, identify recombinant human hyaluronidase as an excipient only.

149 The Commission Implementing Decision, the SmPC, and the EPAR do not show that, recombinant human hyaluronidase has a metabolic, pharmacological, or immunological effect with respect to non-Hodgkin's lymphoma, the therapeutic indication covered by this marketing authorisation. As such, recombinant human hyaluronidase cannot be considered to be an active ingredient under Article 1(b) of the SPC regulation.

150 As a consequence, application SPC/GB16/039 cannot be considered as an application for a combination of two active ingredients, i.e., rituximab and recombinant human hyaluronidase. Rather, it has to be considered as an application for a single active ingredient (rituximab).

151 As this application does not meet the requirement of Article 3(d) of the Medicines SPC Regulation, it is rejected under Article 10(2) of this Regulation.

152 SPC Application SPC/GB16/039 application is thus rejected under Article 10(2) of the Medicines SPC Regulation for failure to meet the conditions laid down in the Regulation.

Other Issues

Status of further submission sent by applicant after the oral hearing

153 Some 8 weeks after the hearing took place, the attorneys wrote to the IPO on behalf of the applicant, including a letter and a review article, in support of their position set out at that hearing. This review article was published in 2021 and I note that one of the authors (A. V. Badkar) is affiliated with the applicant Halozyme. This submission was unsolicited. It was neither (a) in reply to a request for further submissions from the hearing officer, nor (b) addressing a point that arose at the hearing where it was agreed that further submissions were necessary.

154 I consider that I should <u>not</u> accept this submission. It is not appropriate to be providing further materials so late after the hearing and without warning. If I were to accept this submission, what is to say that next time (and referring to the present case as an example), an applicant might submit significantly more material that would require a great deal more time and effort to consider and which had not been presented to the examiner during the examination stage of the case. That cannot be right.

155 The applicant is expected to provide all the materials that are relevant to issues to be decided in advance or at the hearing itself. I have reviewed the transcript and confirmed that an opportunity was provided at the end of the hearing for the applicant and their agent to provide any additional materials or identify if there were any further materials to be submitted.

156 As hearing officer dealing with this case, I did not request any further submissions.

157 At the hearing, when I asked if there were any further matters that they wanted to bring to my attention, the applicant said they had nothing more to add to their case.

158 The agent, in the letter sent with this review article[45], argues that this document is relevant to the discussion at the hearing on "*whether hyaluronidase is necessary for the subcutaneous (SC) administration of Herceptin (or MabThera)*."

159 In case I am wrong in my decision not to accept this submission, for completeness, and because it is a single document that is in question, I will consider the relevance of this review article briefly.

160 This review article does not appear to contain any information that would prompt me to depart from my analysis and conclusions set out above. I consider this review article is consistent with my conclusion – expressed already - that the hyaluronidase is acting as an excipient in the subcutaneous formulation. The hyaluronidase degrades the glycosaminoglycan, hyaluronan, at the local injection side and allows subcutaneous bulk flow which in turn allows the delivery of larger volumes of solution comprising greater amounts of active ingredients than say by intravenous injection (IV).

In my view this further submission provides a more detailed explanation of the role that hyaluronidase plays as excipient in a subcutaneous formulation. I see no reason why (if I am wrong in my decision not to accept this submission and had to do so) this document would lead me to a different conclusion to that which I have already set out above in relation to each of these SPC applications.

Appeal

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

Dr L CULLEN
Deputy Director, acting for the Comptroller

[45] *Review article entitled "Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements" Current Status and Prospect for Future Advancements", AV Badkar et al., Drug Design, Development and Therapy; 2021:15, pages 159–170.*