INTELLECTUAL PROPERTY OFFICE

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

APPLICANT	Imclone Systems Inc. and Aventis Holdings Inc
ISSUE	Whether SPC applications SPC/GB/04/037 and SPC/GB/04/038 comply with Article 3 and may be granted
HEARING OFFICER	Dr L Cullen

DECISION

Introduction

1 This decision relates to two applications for supplementary protection certificates (SPCs) which were filed by Imclone Systems Inc. and Aventis Holdings Inc ("the applicants") on 1 November 2004 and accorded the application numbers SPC/GB/04/037 and SPC/GB/04/038. Application number SPC/GB/04/037 is for the product 'cetuximab in combination with Irinotecan' as indicated at part 6 of Form SP1 filed with the application. Application number SPC/GB/04/038 is for the product 'cetuximab' as indicated at part 6 of Form SP1 filed with the application. Cetuximab is a monoclonal antibody which can be used in the treatment of certain cancers. Irinotecan is an anti-neoplastic drug also used for the treatment of cancer.

2 The basic patent upon which these applications rely is EP (UK) 0667165 B1, which was filed on 15 September 1989, with an earliest priority date of 15 September 1988, and it was granted on 27 March 2002. This basic patent was the subject of a protracted entitlement dispute in the UK which resulted in a decision from the Comptroller in May 2008 transferring the patent into the co-ownership of Yeda Research & Development Co. Ltd & Aventis Holdings Inc. Although the details of the entitlement dispute have no bearing on the present decision, it did mean that matters in relation to the SPC were delayed until after the entitlement dispute was resolved.

3 The marketing authorisation (MA), EU/1/04/28/1/001, for the medicinal product Erbitux supplied in support of the application was granted on 29 June 2004 by Commission Decision C(2004)2509. This marketing authorisation (MA) is thus valid for the UK.

4 The applicant identified the Swiss Marketing Authorisation, granted on 1 December 2003, as the earliest marketing authorisation valid in the European Economic Area as this MA is valid also in Liechtenstein[1]. I note that the title of this marketing authorisation is "*Kombinations Therapie mit cetuximab & Irinotecan",* and, as implied by the title, the language of this authorisation was German and it relates to a combination therapy of cetuximab with Irinotecan. A full translation of this authorisation was not available but the applicant provided a translation of the relevant pages.

5 The view of the Examiner, expressed in his examination reports of 16 December 2004 and 28 July 2009, is that SPC Application SPC/GB/04/037 for the product 'cetuximab in combination with Irinotecan' did not meet the requirements of Article 3(b) of Council Regulation (EC) 469/2009 concerning the creation of a supplementary protection certificate for medicinal products ("the Regulation")[2]. He considered that the marketing authorization supplied is not a valid authorization to place on the market the product identified as being the subject of the application and, as a consequence, it does not meet the condition for the grant of a certificate required under Article 3(b) of the Regulation. The authorisation supplied is for a medicinal product which is identified as having a single active ingredient, cetuximab, whereas the product for which protection is being sought is a combination of active ingredients, cetuximab and irinotecan, only one of which is indicated as being present in the medicinal product covered by the marketing authorisation. Therefore, in his opinion, the authorisation does not relate to the product which is the subject of SPC application SPC/GB/04/037.

6 The view of the Examiner, expressed in his examination reports of 16 December 2004 and 28 July 2009, is that SPC Application SPC/GB/04/038 for the product 'cetuximab' did not meet the requirements of Article 3(a) of the Regulation. He considered that the subject matter protected by the basic patent EP 0667165 is a composition that has two components, a monoclonal antibody such as cetuximab, and an anti-neoplastic agent, such as Irinotecan, that can be used to treat cancer. The product for which protection is being sought in this SPC application is only one of these components, the monoclonal antibody component. Thus, in the examiner's opinion, the basic patent does not protect the specific monoclonal antibody that the applicant has identified as being the subject of the SPC application. The term "product" in Article 3(a) must be interpreted in line with the definition set out in Article 1(b) of the Regulation.

7 On 1 September 2009 the Office wrote to the applicant asking for certain issues in relation to the marketing authorisation for Erbitux to be addressed in written submissions or at the hearing. The applicant filed their skeleton argument and supporting materials on 4 September 2009 and on 7 September 2009 provided a response to the Office letter dated 1 September 2009 and some corrections to their earlier filed materials.

8 These matters came before me at a hearing on 8 September 2009 where the applicant was represented by Timothy Powell and Rebecca Lawrence of Powell Gilbert LLP. The

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[1] MAs granted in Switzerland can also have effect in Liechtenstein which is one of the EEA member states and thus may serve as the first MA in the Community, see joined cases ECJ C-207/03 and C-252/03.

[2] This is a codification of Council Regulation (EEC) 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products which had been substantially amended several times, which it supercedes. Annex II to Regulation 469/2009 indicates the correlation between the recitals and Articles in Regulation 1768/92 and those in 469/2009

examiner Dr Patrick Purcell also attended.

9 At the hearing, Mr Powell indicated that although his client wished to maintain both applications, he acknowledged that SPC/GB/04/038 appeared to have a lesser chance of success given current case law and practice than SPC/GB/04/037. He proposed to argue the issues in relation to SPC/GB/04/037 first and then consider those in relation to SPC/GB/04/038.

SPC APPLICATION SPC/GB/04/037 FOR THE PRODUCT "CETUXIMAB IN COMBINATION WITH IRINOTECAN"

The Relevant Case Law and its Interpretation

10 Article 3 of the Regulation defines the conditions for obtaining a certificate (emphasis added):

> **"Article 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) the product is protected by a basic patent in force;**
>
> **(b) a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC or Directive 2001/82/EC, as appropriate;**
>
> (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"

11 Article 1 of the Regulation provides definitions for these terms as follows:

> "**Article 1**
>
> For the purposes of this Regulation, the following definitions shall apply:
>
> (a) 'medicinal product' means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;
>
> (b) 'product' means the active ingredient or combination of active ingredients of a medicinal product;
>
> (c) 'basic patent' means a patent which protects a product as such, a process to obtain a product or an application of a product, and which is designated by its holder for the purpose of the procedure for grant of a certificate;
>
> (d) 'certificate' means the supplementary protection certificate."

12 Thus for the purposes of the Regulation, the term "product" means the active ingredient or combination of active ingredients of a medicinal product whilst the term "medicinal product" refers to any substance or combination of substances presented for treating or preventing disease in human beings of animals. This makes clear that certificates are not granted for the medicinal product but rather for the active ingredients present in a medicinal product. Article 1(c) makes clear that the basic patent must protect the product.

13 The interpretation of Articles 1(a) and (b) was set out in *Draco A.B.'s SPC Application* [1996] RPC 417. The importance of the definitions provided by Articles 1(a) and 1(b) and the role of the marketing authorisation was considered by Jacob J as he then was. He noted that the distinction made in these definitions must also be applied in reading recitals 8 and 9 and thus he makes clear that the protection granted by a certificate is strictly confined to the active ingredient which is presented for treatment. At page 438, lines 30 to 35 of his judgment, he stated:

> "*It will be noted that the two recitals use both the phrase medicinal product and product. Without more there could be ambiguity. This is because authorisations typically are not for active ingredients as such. They are much more tightly drawn, generally to dosage and formulation or presentation. That has to be so because the actual performance of an active ingredient depends on these matters in addition to the active ingredient itself.*"

He went on to note that the authors of the Regulation had thought about the difference between the active ingredient and the actual formulation, and in so doing had defined "medicinal product" and "product" in Article 1. He then stated at page 439, lines 1 to 5:

> *"I have no doubt, nor do I think anyone else would have any doubt, that recitals 8 and 9 must be read as using these definitions. So strictly confined to the product which obtained authorisation means: strictly confined to the active ingredient of that which is presented for treatment."*

14 As a result the protection afforded by a certificate extends only to the product (the active ingredient or combination of active ingredients) covered by the authorisation to sell the corresponding medicinal product. Thus, it is clear that a marketing authorisation for a medicinal product which comprises a single active ingredient does not meet the condition for grant laid down by Article 3(b) in the situation where an SPC is sought for a combination of active ingredients. The converse is also true as a marketing authorisation for a medicinal product which comprises a combination of active ingredients does not meet the condition for grant laid down by Article 3(b) in the situation where an SPC is sought for a single active ingredient.

15 More recently Lord Justice Jacob has again considered the interpretation of the Regulation and Article 1 especially in the Court of Appeal decision in *Generics UK v Daiichi*, 2009 EWCA CIV 646. At paragraph 58 he states:

> *"58. In the Regulation "product" means "the active ingredient or combination of active ingredients" (Art.2(b)). Clearly that must be read with the words "as the case may be" at the end. If you have two active ingredients the "product" is the pair of them. And ofloxacin is a combination of significantly active ingredients. So it is that combination which was the subject of the 1990 and 1985 authorisations. The authorisation for levofloxacin was the first authorisation for that active ingredient alone."*

16 It is clear that Jacob LJ considers that when a medicinal product is a combination of actives then, for the purposes of the Regulation, it is that combination which is the product as defined by Article 1(b) and for which a certificate could be granted. The corollary is thus also true, where the medicinal product is a single active ingredient then

for the purposes of the Regulation it is that active ingredient which is the product as defined by Article 1(b) and for which a certificate could be granted

17 Further Article 4 of the Regulation defines the subject matter of protection of a certificate in the following terms:

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

Thus whilst the protection is within the limits of the patent, it "*extends only to the product covered by the authorisation...*" and so it is apparent that it is not possible to break up a combination into its component parts.

Analysis & Argument

18 In order to determine if the requirement of Article 3(b) is met, it is essential to establish what is the medicinal product that has been authorised by the marketing authorisation and then to determine what is the active ingredient or active ingredients in that medicinal product.

19 In order to do so, I would first like to clarify the exact status of the various substances referred to in this case. Erbutix is the medicinal product described in EU/1/04/28/1/001. Erbutix comprises the monoclonal antibody, cetuximab, as well as a number of other substances (i.e., excipients) which, when these are all put together, make up this medicinal product. References in the text of the marketing authorisation to irinotecan are to Irinotecan as a medicinal product, i.e., to a product as defined under Article 1(2)(a) and (b) of the Directive which is the same definition of medicinal product as that in Article 1(a) of the Regulation, i.e. a substance presented for use in treating disease in humans with all the necessary excipients etc. to allow it to be so presented. Thus, Irinotecan is not a product according to Article 1(b) of the Regulation, it is not the active ingredient or combination of active ingredients in the medicinal product Erbutix. At best, it may contain, the product irinotcean as the active ingredient in the medicinal product Irinotcean but I do not have any details about this medicinal product or the relevant MA other than the references made to it in the MA for Erbutix. I have adopted the convention of using a capital letter to denote the medicinal product, i.e. Erbutix or Irinotecan and a lower case letter when denoting the product, i.e. cetuximab or irinotecan.

20 This is an important issue in relation to the discussion below because the applicant refers to the MA filed in support of this application as being an authorisation for the combination of the products cetuximab and irinotecan. On the basis of the above definitions, the applicant is referring to the use of the medicinal product Erbutix in conjunction with the medicinal product Irinotecan to achieve a useful therapeutic outcome. The applicant would appear to consider that this is a justification for claiming this is an authorisation for a combination of the products cetuximab and irinotecan. I do not consider that it is – all references below to cetuximab and irinotecan are to the use

of the medicinal product Erbutix and the medicinal product Irinotecan.

Marketing Authorisation EU/1/04/28/1/001

21 The marketing authorisation (MA) filed in support of these SPC applications was EU/1/04/28/1/001 granted by European Commission Decision C(2004)2509 on 29 June 2004 for the medicinal product Erbitux, which comprises the monoclonal antibody cetuximab.

22 The granting of MAs to place medicinal products for human use on the market in the EU is governed by Directive 2001/83/EC (hereafter referred to as the Directive)[3] which lays down the type of information that an applicant for an MA must provide and the requirements that they must meet in order to gain marketing approval. This applies to medicinal products which are being authorised by national competent authorities such as the MHRA[4] in the UK, or by the central European body, the EMA, the European Medicines Agency[5]. The procedures followed by the EMA in deciding whether or not a medicinal product can be approved are laid out in EC Regulation 726/2004[6]. The EMA makes recommendation following an assessment of the quality, safety and efficacy of the medicinal product based on the data submitted by the applicant for the MA. This recommendation is the basis on which the Marketing Authorisation is granted by the European Commission. Information on medicinal products that have been approved by the EMA and the products (i.e. active ingredients) they contain is available from the EMA website[7] including the information on Erbitux[8]. Providing such information to the general public in an accessible and useful form is one of the objectives of the EMA under EC Regulation 726/2004[9].

23 An MA lasts, in the first instance, for a period for 5 years and then the applicant must apply for a renewal. In the course of its life, the MA may also undergo a number of changes as new therapeutic uses and new physical forms of the medicinal product are approved (see discussion below). At the date of the hearing, this authorisation, EU/1/04/28/1/001, had been renewed once by European Commission in Decision C(2009)5201 of 17 June 2009. Both the current version of the MA and the version that existed when the SPC was applied for were included in the papers supplied for my consideration at the hearing.

24 At the hearing, Mr Powell directed my attention to the version of the marketing authorisation that was approved and in existence on the date that the applicant applied for SPC/GB/04/037 for the combination of cetuximab and irinotecan. He drew my attention to various passages which in his view indicated that the medicinal product,

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[3] 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 (OJ L 311, 28.11.2001, p. 67)
[4] Medicines & Healthcare products Regulatory Authority (MHRA), see www.mhra.gov.uk.
[5] See www.ema.europa.eu, (formerly, and still often, referred to as the EMeA or EMEA or The European Medicines Evaluation Agency or the European Agency for the Evaluation of Medicinal Products)
[6] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p 1)
[7] See http://www.ema.europa.eu/htms/human/epar/eparintro.htm.
[8] The details for Erbitux, referred to as an EPAR (European Product Assessment Report), can be found at http://www.ema.europa.eu/humandocs/Humans/EPAR/erbitux/erbitux.htm .
[9] see Article 57 of Regulation 726/2004.

which comprises the active ingredient cetuximab, was only approved for use with another medicinal product Irinotecan, i.e., that it was approved for use as a combination of active ingredients.

25 Mr Powell then went on to illustrate why this was the case. When the application was made, Article 1 of decision C(2004)2509 indicates that the MA was for the medicinal product "Erbitux – cetuximab" whose characteristics were defined in Annex 1 to the decision. In Annex I, I was directed by Mr Powell to take particular note of Section 4, parts 4.1, 4.2 and 4.5 (see pages 2 & 4) of the Summary of Product Characteristics (SmPC) and I reproduce some of this text below:

> "Erbitux in combination with Irinotecan is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of Irinotecan-including cytotoxic therapy. (from part 4.1)"
>
> For the dosage of concomitant Irinotecan, refer to the product information for this medicinal product. Normally the same dose of Irinotecan is used as administered in the last cycles of the prior Irinotecan-containing regimen. However, recommendations for the dose modification of Irinotecan according to the product information of ths medicinal product must be followed. Irinotecan must not be administered earlier than 1 hour after the end of the cetuximab infusion. Irinotecan must not be administered earlier
> than 1 hour after the end of the cetuximab infusion. (see part 4.2)
>
> There is no evidence that the safety profile of cetuximab is influenced by Irinotecan or vice versa.
>
> A formal interaction study showed that the pharmacokinetic characteristics of cetuximab remain unaltered after co-administration of a single dose of Irinotecan (350 mg/m^2 body surface area). Similarly the pharmacokinetics of Irinotecan were unchanged whem cetuximab was co-administered. (see part 4.5)"

26 Mr Powell also directed me to note that Article 3 of the decision specified that the labelling and package leaflet concerning the medicinal product should conform to Annex III to the decision. In Annex III, I was directed to take account of Sections 1, 2 and 3 of 'Part B. Package Leaflet' (see pages 19 & 20). These passages all indicate, in Mr Powells view, that Erbitux is approved for use in combination with Irinotecan. They remind the reader that "Erbutix is used in combination with this medicine Irinotecan" and that they should also read the package leaflet for Irinotecan. It also says that Irinotecan must not be given to the patient earlier than 1 hour after administration of Erbitux.

27 Mr Powell also indicated that the MA makes clear that Erbitux has a therapeutic activity in relation to cancer. It shows cytostatic activity in relation to certain cancers of the colon and/or rectum, i.e. it stops/hinders cell growth in cancers. Irinotecan also has a well established therapeutic activity of its own in relation to cancer – it is cytotoxic. This is referred to, for example, in the text reproduced above from Section 1, part 4.1 of the SmPC. Mr Powell considered that this means that the present application meets the definition of a combination of active ingredients under Article 1(b) of the SPC Regulation as elaborated by the ECJ in C-202/05 *Yissum*[10] and C-431/04 *MIT*[11]. Erbitux and Irinotecan both show therapeutic activity against cancer and so represent a combination therapy. The present situation can be distinguished from that in *MIT* where

[10] C-202/05, Yissum Research & Development Company of Hebrew University of Jerusalem v Comptroller-General of Patents, see also [2004] EWHC 2880 (Pat)
[11] C-431/04, Re Massacheusetts Institute of Technology, see also [2006] RPC 34

the second active ingredient in the claimed combination SPC product definition did not have any therapeutic activity against cancer, as did the first active ingredient claimed, and it only controlled the rate or release of the first active ingredient in the claimed combination.

28 In further support of this argument Mr Powell made reference to the detailed 47 page report reporting the scientific discussion at the EMA in relation to the approval of Erbitux which was also provided for my consideration at the hearing[12]. In particular he referred me to the following paragraphs (from pages 1 and 41) of the report which state:

> **"1. Introduction**
> Erbitux contains the active substance cetuximab, a chimeric monoclonal antibody of the immunoglobulin G1 (IgG1) class that is directed against the human epidermal growth factor receptor (EGFR). With the present application, the applicant sought a marketing authorisation for Erbitux, either in combination with Irinotecan or as a single agent, for the treatment of patients with EGFR expressing metastatic colorectal cancer after failure of Irinotecan-including cytotoxic therapy. Following the assessment of the documentation submitted, the CPMP expressed doubts on whether there was sufficient evidence to establish a positive benefit risk profile for Erbitux as a single agent treatment in the applied indication. Subsequently, the applicant restricted the indication for Erbitux to the combination treatment with Irinotecan. The scientific discussion in this report focuses on this indication. *(page 1)*
>
> …….Strong synergistic effects were observed when cetuximab was combined with Irinotecan compared to the tumor growth control exerted by the single agents. *(page 1)*
>
> **Recommendation**
> Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Erbitux in combination with Irinotecan in the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of Irinotecan-including cytotoxic therapy was favourable and therefore recommended the granting of the marketing authorisation. *(page 41)*"

29 Bringing all this material together, Mr Powell argued that this clearly indicates that the only product that was approved when the MA was granted in 2004 was a combination of Erbitux with Irinotecan and that there was not enough evidence to show that Erbitux as a monotherapy should be approved. He suggested that if a doctor had suggested using Erbitux on its own they would have been prescribing a medicine that was not approved for use in humans at that time.

30 However, I do not consider that this is the full story, and it is necessary for me to take a wider view than this when considering the medicinal product that is approved by this marketing authorisation.

31 Article 8(3) and Annex I of the Directive indicate all the information that the application for the MA must contain, for example, what are the ingredients of the medicinal product, what is its physical form, route of administration, strength and dose level, what is its therapeutic effect and any side-effects or situations where it should not be used. Article 1 of the Directive makes clear that a medicinal product cannot be sold for human use in the EEA unless it has been authorised under this Directive. It is clear from Article 6 that

[12] This report of the scientific discussion can be found on the EMEA website under the entry for Erbitux in the section entitled "EPARs (European Public Assessment Reports) for authorised medicinal products for human use" referred to in footnote 6 above, see http://www.ema.europa.eu/humandocs/PDFs/EPAR/erbitux/089404en6.pdf

the MA is for the medicinal product and that new physical forms e.g. new strengths, administration routes and presentations (i.e., new physical forms such as lozenge, tablet, solution, powder) and new therapeutic uses, e.g. new variations or extensions, can also be included in this authorisation as they are approved by the relevant authorising authority. This approval will be based on the necessary data (as referred to in Article 8 and Annex I) being submitted to the authority by the holder of the MA to show that medicinal product is safe, effective and beneficial when used in humans.

32 The granted MA relates to a medicinal product that has been found to be effective for use in humans in the first instance in one particular situation (described in Commission decision C(2004)2509), i.e., if it is administered to patients who have a particular type of colorectal cancer that have failed to respond to treatment with Irinotecan alone, when Erbitux is given to these patients and a period of time is allowed to elapse before they are given Irinotecan, the response to Irinotecan is much improved – the cancers now respond to treatment with Irinotecan.

33 If, as Mr Powell asked me to do, I consider the MA as it was when the SPC application was filed, i.e., in decision C(2004)2509, the attached SmPC makes clear that the medicinal product that is the subject of the authorisation is Erbitux and that it contains cetuximab as the active ingredient. The title of the decision refers to "Erbitux – cetuximab" alone and not to a combination of Erbitux and Irinotecan. The medicinal product is clearly identified as Erbitux, the active ingredient is cetuximab, the physical form is a solution for infusion – see Sections 1, 2 & 3 of the SmPC. This data does not change and defines clearly what is the medicinal product and the active substance which is the subject of the MA. This is in my view distinguishable from how this medicinal product is used. This can change on the basis of further clinical evidence and experience and this will happen over the life of an MA. It is only those parts of the MA that deal with the use of Erbitux in patients that mention Irinotecan. The MA is otherwise silent on Irinotecan, its use, constituents, safety, etc. In those parts of the MA that define the medicinal product in terms of quality or safety, e.g. describing how it is prepared and what are its components, there is no mention of Irinotecan. For example, Section 2 of the SmPC annexed to decision C(2004)2509 states:

> "Each ml of solution for infusion contains 2 mg cetuximab. Each vial contains 50 ml.
>
> cetuximab is a chimeric monoclonal IgG antibody produced in the mammalian cell line (Sp2/0) by recombinant DNA technology
>
> For excipients, see Section 6.1"*;*

and, Section 6 of the SmPC, entitled '*Pharmaceutical Particulars*' does not make any mention of Irinotecan as being a component of this medicinal product. Thus, Irinotecan is not present in any way in the medicinal product that has been approved by this MA.

34 I consider that this latter point is an important and relevant one because, as I have indicated already, the MA must be considered as an entire document. The passages of the SmPC brought to my attention by Mr Powell all relate to how the medicinal product Erbutix can be used in a clinical situation to give a good therapeutic effect, i.e. focus solely on the efficacy of the medicinal product Erbutix.

35 Further uses of Erbitux (e.g., as a mono-therapy or in combination with other drugs or treatments) have been approved since the first authorisation and in the period 2004-

2009, the MA for Erbitux has undergone a number of changes (24 in total) which have resulted in this medicinal product being approved for use both on its own and in conjunction with other known active agents[13]. The current version of the MA for Erbitux (see decision C(2009)5201) shows that it has therapeutic benefits in an increased number of cancer treatments, i.e., cancer of the head and neck in addition to cancer of the colon and rectum and can be used as both a mono-therapy on its own, in combination with radiation treatment and in combination with other platinum based cancer drugs as well as Irinotecan. When used in combination with any other drugs the SmPC indicates that the Erbitux is administered first then, at least, 1 hour is allowed to pass before the other cancer drug is administered. Thus the original interaction that Erbitux has with cancer cells that lead to Irinotecan being more effective when applied at least 1 hour later is one that applies in a number of other cancer treatments. In addition, Erbitux has also subsequently been found in certain circumstances to have a therapeutic effect when administered on its own for the treatment of colon cancer (see Section 4 'Clinical Particulars', para 4.1 'Therapeutic Indications', of SmPC annexed to Commission Decision C(2009) 5201). This confirms in my view that the MA cited as the basis for SPC application SPC/GB 04/037 is for Erbutix on its own and not for Erbutix and Irinotecan.

36 The report of the scientific discussion on the approval of Erbitux to which Mr Powell refers, also describes more than just the clinical use (i.e., the therapeutic indication) of this medicinal product as a specific cancer therapy. This report comprises 47 pages and thus comprises further data in addition to that highlighted by the applicant. The report discusses in detail what is the active ingredient (i.e., cetuximab), what form the medicinal product Erbutix is available in, what additional materials are included in this medicinal product, how it is made, how it is stored etc., what is its mechanism of action, how this is studied and assessed, whether it has any side effects or causes problems of complications. The discussion of how this medicinal product is used therapeutically is only a part of the overall discussion of the quality, safety and efficacy of a medicinal product. This discussion does indicate that on the basis of the clinical evidence filed that while Erbutix does have therapeutic activity on its own, the benefit/risk profile (as defined in Article 1, Sections 28 and 28a of the Directive) of this mono-therapy was not favourable whereas if Erbutix is used as an add-on with patients who are failing treatment with the medicinal product Irinotecan, the benefit/risk profile is favourable and thus a MA can be granted for Erbutix indicating this use of Erbitux as a suitable treatment.

37 I consider that the discussion of how Erbitux is used therapeutically is only part of the overall discussion of the quality, safety and efficacy of a medicinal product such as Erbitux which make up the approval process for the grant of the MA as outlined in Directive and in Regulation EC 724/2004. This process is about making sure that a medicinal product is safe to use and that it has no unexpected side effects from its manufacture, storage or use, as well as, confirming that it has a sufficient therapeutic effect in treating a specific illness or disease. Thus, in this case, the assessment of

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[13] The history of these changes, the related authorisation procedures at the EMA and copies of the various decisions of the Commission authorising changes to this MA can be followed from the entry for "Erbutix – cetuximab" from the Community Register of Medicinal products for Human Use (found at http://ec.europe.eu/enterprise/pharmaceuticals/register/h281.htm).

quality, safety and efficacy does not only just relate to the therapeutic use of Erbitux to treat cancer of the colon and rectum. As a consequence, it is not only the information under the clinical particulars, i.e. Section 4 of the SmPC, that are relevant in deciding what medicinal product and hence what active ingredient the MA approves. As I have said above, all the information in the MA is relevant not just those parts which support a particular therapeutic use. Furthermore, the MA is not limited to a particular clinical use. It is, in effect, a living document that covers this clinical use and any other clinical use that is approved by the competent authority for this medicinal product.

38 Article 4 of the Regulation recognises the fact that other therapeutic uses of the product, comprising the active ingredient covered by the SPC, may be authorised. The SPC is not limited to the first approved use or the use that was approved when the application for the SPC was made because the SPC will also protect any future use or uses that this product in any medicinal product may be approved for after the original approval has been granted, within the limits of protection provided by the basic patent on which the SPC relies (see Article 5 of the Regulation).

39 When questioned Mr Powell acknowledged that the MA for Erbitux has subsequently been updated to include uses where Erbitux is used on its own, i.e., as a mono-therapy, and in other combinations. This has happened as additional data has emerged to show new therapeutic uses of Erbitux. However, he considered that this was not relevant to the decision that I am being asked to make and I need to take account only of the situation when the application for the SPC was made. While I agree that I must only consider if the product referred to in the SPC application is the active ingredient in a validly authorised medicinal product on the date that the SPC was applied for, I cannot ignore the fact that the SPC will also cover future approved uses of the medicinal product. In this case, I find that a consideration of the changes to the MA between Commission Decisions C(2004)2509 and C(2009)5201 is helpful in deciding whether this MA is for the medicinal product Erbutix or for Erbutix and Irinotecan.

40 According to Article 1(a) of the Regulation, a medicinal product is defined as a 'substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances that may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals'. In my view, the MA filed in support of this SPC application only comprises complete information regarding the quality, safety and efficacy of one medicinal product or substance – Erbitux – and one product or active ingredient in that substance – cetuximab. It is clear from the original MA for Erbitux that the other medicinal product – Irinotecan – is the subject of a different MA and the reader is directed to consult that MA for details. Thus, despite the view put forward by Mr Powell, I consider that the passages he referred me to in the SmPC, and the assessment report, do not tell the full story. They describe conditions under which Erbitux may be used clinically. I have to concern myself with determining what exactly is the medicinal product that has been approved and not just with its use or uses. Furthermore, such a focus on what the product is, rather than what it does, is consistent with the fact that what it does can change in the life of the MA but the product itself does not. In my view the MA for Erbitux is not one for a medicinal product that is a combination of substances rather it is one for a single substance. Thus the corresponding product which is approved in terms of Article 1(b) of the Regulation is a single active ingredient, cetuximab. The MA for

'Erbitux' allows the holder to place this medicinal product on the market and so is the first for the active ingredient 'cetuximab'. It is not one for the combination of "cetuximab in combination with Irinotecan".

41 It is apparent in this case and in a number of recent decisions from the Office[14], the use of the term 'combination' to describe the product for which the SPC is being sought has been problematic. This term is being used to describe any one of a number of ways to bring two or more components together which have therapeutic effect. In the present case, what is being described in the MA is a way to use the medicinal product Erbutix in therapy, i.e. Erbutix can be used in a way to improve how other agents work. It does not have to be given in a fixed dose with another agent, it just has to be administered first so it can exert its effect and then the second medicinal product, in this case Irinotecan, can be administered and it can exert its effect, a different one to Erbutix, but one which is improved because the Erbutix has been given first. This is not in my view the same as describing a combination product. I would expect the components in a combination product to be defined in detail in the same marketing authorisation. Thus if the present MA is as Mr Powell argues an MA for the combination product of cetuximab and irinotecan rather than one for the product cetuximab, it needs to provide greater detail about the irinotecan. In my view Articles 6-12 of the Directive indicate that a medicinal product is the subject of a single MA[15] and Articles 6(1) and 8(3), in particular, in my view, indicate that a marketing authorisation must contain all the information about the medicinal product in the application when it is made. Including information on one of the components by reference to an earlier or different MA does not, in my view, meet the requirement to provide all the information about the medicinal product being authorised and such a reference points away from any such component being considered an integral part of the medicinal product authorised by the present MA.

42 Thus, I do not consider that the use of Erbitux and Irinotecan as a combination therapy is the same as saying that Erbitux and Irinotecan are a combination medicinal product or a combination of active ingredients in a medicinal product. In the present case, we are given details of how to get the best clinical use out of Erbutix. In the SmPC at page 2, Section 4 "Clinical Particulars" section 4.2 it indicates that patients should receive a premedication with an antihistamine prior to the first infusion with "Erbitux" and that such treatment is recommended for subsequent uses of "Erbitux". Irinotecan should be administered at least one hour after the "Erbitux" infusion has been completed. This protocol for the use of "Erbitux" is also reiterated at, for example, Annex III, page 20, Section 3 "How to use Erbitux" of the "Package leaflet" information. Indeed at page 22 of this Annex there are clear instructions that "It must not be mixed with any other intravenously applied medicinal products." These are in my view steps designed to get the best effect from the use of Erbitux as a cancer treatment. Thus, whilst there is a link between how the medicinal products containing cetuximab and irinotecan are used in treating cancer it does not mean that the actual combination has been authorised itself by this MA. It does not, for example, require that "cetuximab" is put on the market in combination with "irinotecan" in a particular ratio of one component to another or

[14] See, for example, BL O/401/09 and BL O/357/09 where use of the term combination in relation to vaccines is argued to have a different meaning to that in relation to non-vaccines as many active components which each have activiteis against different diseases are administered in a single dose; see BL O/052/09 which relates to a combination which comprises fixed amounts of two components , details of both are provided in full detail in the cited MA

[15] The language used in these articles is singular, e.g., Articles 6(1) and 8(3).

describe how the components of the combination should be combined together to create a medicinal product. As I have discussed above, the MA does not provide anything like the same level of information about irinotecan as it does about cetuximab. I consider that this points away from the idea that the present MA is one for a combination product.

43 As far as I am aware, but I was not addressed on this point, an MA for a combination product will indicate quite clearly what the ratio of the components are, how they interact, how the combination is prepared. For example, I am aware that the medicinal product *Atripla,* that is approved for the treatment of HIV, is a combination of three active ingredients in a single tablet and the MA indicates that this is a medicine containing a combination of 3 active substances in a fixed ratio to each other delivering a fixed dose[16].

44 The consequence of accepting Mr Powells view that the interpretation of the MA as filed with the SPC application is a suitable authorisation under Article 3(b) of the Regulation to justify grant of the SPC application for the combination of cetuximab and irinotecan, is that this would lead to uncertainty regarding what medicinal product is approved by this MA. The MA provides a complete set of data in relation to Erbutix which comprises cetuximab and provides practically no data about Irinotecan. The data on Irinotecan can only be obtained from the MA for that medicinal product. Thus the SPC being sought would appear to require account to be taken of two MAs when considering if it meets the requirements of Article 3(b). This is, in my view, not what the regulation intended, each SPC application relates to a single marketing authorisation and a single patent and if more than one patent or MA are required, then the SPC application does not meet the requirements of Article 3 of the Regulation.

45 Also, I cannot only consider the date of the SPC application as a cut-off date for determining what product was approved by the MA. I have to take account of the MA as a whole and acknowledge that it can change with time. The question to be determined, based on the definitions in Article 1 of the Regulation, in my view, is what medicinal product i.e. substance or combination of substances that have therapeutic effect in humans, does the MA, considered in its entirety, approve for human use and, in turn, what is the active ingredient or combination of active ingredients in that medicinal product that is capable of protection by an SPC.

46 I find support for my interpretation in the *Draco* decision referred to above and recital 10 of the Regulation. In considering the definitions in Article 1(a) and 1(b) and recitals (8) and (9) as they then were, (now recitals (9) and (10) of codified regulation EC 469/2009), Jacob J, as he then was in *Draco*, noted the protection granted by a certificate is strictly confined to the product (i.e., active ingredient) in the medicinal product that has been approved for human use. On the basis of this and the decisions referred to above in *MIT* and *Yissum*, I consider that the therapeutic use that has been approved is not the determining factor as this may change with time but rather what is the exact medicinal product that has been approved and what is the product, i.e., the active ingredient, in this medicinal product that is capable of protection by an SPC. This leads me to the view that I cannot just take account of the clinical particulars of the

[16] Atripla is a medicine containing three active substances: efavirenz (600 mg), emtricitabine (200 mg) and tenofovir disoproxil (245 mg). It is available as pink, capsule-shaped tablets. See http://www.ema.europa.eu/humandocs/PDFs/EPAR/atripla/emea-combined-h797en.pdf

authorised product but rather I have to consider all the details in the MA to decide exactly what is the product that can be protected by an SPC.

Relevance of Swiss Authorisation as first authorisation in the community (see Article 3(d) of the Regulation)

47 In coming to the view that I have above in relation to the MA that is valid in the UK being for the medicinal product Erbitux comprising the active ingredient cetuximab alone, I find that I must examine the relevance of the Swiss MA identified by the applicant on form SP1 submitted with their application as the earliest authorisation for the combination of Erbitux and Irinotecan in the EEA.

48 Mr Powell pointed out at the hearing that the MA that had been approved by the Swiss national authorities for a combination of Erbitux and Irinotecan was, in effect, the same as the MA approved by the EMA because it was based on exactly the same evidence. Mr Powell also mentioned that in the course of the approval process that Swiss authorities considered that the title of the Swiss authorisation should be amended to make it clear that the approval was for the combination therapy only. Thus I am satisfied that a Swiss MA referring to this combination is one that should be notified to the UK Office as being relevant under Article 3(d) and Article 13 for the calculation of the term of the SPC in relation to SPC application SPC/GB/04/037 which is for such a combination product. However, as I have indicated above, I do not consider that the MA which is valid in the UK and cited in support of this SPC application is one that approves the combination product, it approves only Erbitux on its own.

49 Thus the situation has arisen where two authorities would appear to have come to a different conclusion based on the same facts – the Swiss competent authority consider that approval could be granted only for the combination of Erbutix, which comprises active ingredient cetuximab, with Irinotecan. As a result they required that the title of the MA be altered accordingly – as indicated by the translations of the French and German entries on the Swissmedic website in relation to this approval provided by the applicant in the bundle of papers for the hearing:

> '*the preparation Erbutix is approved for indication/possible use "in combination with irinotecan for the treatment of patients with EGFR-expressing metastising colorectal carcinoma when a cytotioxic therapy including irinotecan has failed*"'

50 I also note that this translation clearly indicates that "*questions relating to the marketing authorisation of the monotherapy* (i.e. Erbutix on its own) *now form a separate procedure*" (emphasis as underline added by me).

51 The EMA did not reach the same conclusion; the medicinal product they approved was Erbutix, comprising cetuximab, alone. Clearly, the EMA concluded that granting an MA for Erbutix alone was justified and did not see a basis for refusing an MA on the same facts. I assume, but I was not addressed specifically on this point, that the EMA could have chosen to indicate if the combination only should be approved. They do not appear to have done so, e.g., by refusing the MA for Erbutix. However, in the scientific discussion referred to by Mr Powell (see para 25 above), the EMA did note that the use of Erbutix with irinotecan was more beneficial that the use of Erbutix on its own and that the applicant had decided to restrict the application to the indication where Erbutix is being used in combination with irinotecan. However, as I have indicated above,

consideration of the clinical particulars in the SmPC attached to the MA is only part of the determination of what is the authorised product and hence the product that can be protected by an SPC.

52 In relation to this point, I note that the Swiss MA is granted under its national law as Switzerland is not an EEA state and is relevant for the purposes of Article 13 of the SPC Regulation concerning the duration of the SPC by virtue of the fact that Swiss MAs are valid in Liechtenstein which is an EEA state. Thus there may be some differences in how they approach the granting of an MA in comparison to that of the EMA although both systems are based on very similar legislative provisions. However, as the MA granted by the EMA is the one that is valid in the UK and determines whether or not an SPC application meets the requirements of Article 3(b), this is the one that I must take into account.

SPC APPLICATION SPC/GB/04/038 FOR THE PRODUCT 'CETUXIMAB'

The Relevant Case law and its Interpretation

53 The ECJ has previously considered the interpretation of Article 3(a) of the Regulation in *Farmitalia Carlo Erba Srl's SPC Application*[17] and the court concluded that the question of what is protected by a patent is not harmonised at EC level and is therefore a matter for national law.

54 As regards domestic patent law, section 125 of the Patents Act 1977 determines how the scope of an invention is to be determined. The relevant subsections read as follows:

> "(*1) For the purposes of this Act an invention for a patent for which an application has been made or for which a patent has been granted shall, unless the context otherwise requires, be taken to be that specified in a claim of the specification of the application or patent, as the case may be, as interpreted by the description and any drawings contained in that specification, and the extent of the protection conferred by a patent or application for a patent shall be determined accordingly.*
>
> *(2)…*
>
> *(3) The Protocol on the Interpretation of Article 69 of the European Patent Convention (which Article contains a provision corresponding to subsection (1) above) shall, as for the time being in force, apply for the purposes of subsection (1) above as it applies for the purposes of that Article."*

55 Both Article 69 of the EPC and section 125(1) of the Act should be construed in the light of the Protocol on the Interpretation of Article 69 of the EPC, which reads:

> "*Article 69 should not be interpreted in the sense that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, literal meaning of the wording used in the claims, the description and drawings being employed only for the purpose of resolving an ambiguity found in the*

[17] ECJ Case C-392/97, re Farmitalia Carlo Erba Srl SPC Application, see also [2000], RPC, 580

claims. Neither should it be interpreted in the sense that the claims serve only as a guideline and that the actual protection conferred may extend to what, from a consideration of the description and drawings by a person skilled in the art, the patentee has contemplated. On the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patentee with a reasonable degree of certainty for third parties".

56 There is extensive case law on the interpretation of these provisions which govern precisely how patent claims should be construed. All are concerned with the principle that patent claims have to be read in the light of the description and may not always be accorded their literal interpretation. However it is important to appreciate that the purpose of the claims in a patent is to delimit the scope of the monopoly conferred by the patent, and the law on claim construction has developed with that in mind. Accordingly, patent law does not itself have any need for a notion of what is "protected" beyond a consideration of the proper construction of the claims for the purposes of determining what is, or is not, infringing or impugning of patentability.

57 Therefore I need to consider specifically the case law on the interpretation of Article 3(a) in order to determine what is the meaning of "protected". In *Takeda Chemical Industries Ltd's SPC Applications (No.3)*, [2004] RPC 3, hereafter referred to as *Takeda*, which concerned SPC applications for products which were combinations of lansoprazole, which was specified in the nominated basic patents, and certain other antibiotics which were not mentioned in the basic patents, Jacob J commented (at paragraph 10):

> *"In truth, the combination is not as such "protected by a basic patent in force". What is protected is only the lansoprazole element of that combination. It is sleight-of-hand to say that the combination is protected by the patent. The sleight-of-hand is exposed when one realises that any patent in Mr Alexander's sense protects the product of the patent with anything else in the world. But the patent is not of course for any such "combination"."*

58 I find these comments to mean that everything that infringes the basic patent is not necessarily protected by it. Therefore *Takeda* does not readily assist me to determine the meaning of the word 'protected' as used in the Regulation.

59 The question of what the term 'protected by the basic patent' in Article 3(a) meant was further considered in *Gilead Sciences SPC Application* [2008] EWHC 1902 (Pat), hereafter referred to as *Gilead.* Kitchin J considered *in obiter* whether the approach of *Takeda* was correct and he did not disagree with it. He then went on to find that:

> *"33. … I believe a test emerges from Takeda which is clear and can be applied without difficulty to a product comprising a combination of active ingredients. It is to identify the active ingredients of the product which are relevant to a consideration of whether the product falls within the scope of a claim of the basic patent. It is those ingredients, and only those ingredients, which can be said to be protected within the meaning of the Regulation. So, in the case of a product consisting of a combination of ingredients A and B and a basic patent which claims A, it is only A which brings the combination within the scope of the monopoly. Hence it is A which is protected and not the combination of A and B."*

Thus at the heart of this test is an analysis of the claim in the basic patent alleged to protect the product.

60 The question of whether a patent protects an active ingredient has recently been considered further by this hearing officer in *Astellas Pharma Inc*., BL O/052/09. In this decision, taking account of both *Takeda* and *Gilead*, this hearing officer found that a claim to a single active ingredient, empodepside, did not protect a combination of active ingredients, empodepside and praziquantel, present in a medicinal product Profender, as there was no disclosure anywhere in the claims or description to suggest that a combination product was envisaged. This decision was appealed and in his judgement, see *Astellas Pharma Inc* [2009] EWHC 1916 (Pat), Arnold J upheld the decision of this hearing officer and found that, where the basic patent does not disclose and claim a combination of active ingredients, that combination cannot be considered to be protected by the basic patent within the meaning of Article 3(a). He also held that a claim to an active ingredient which used the term "comprises" means the claim *covers* products which include substances other than the claimed ingredient without having to disclose them (see paragraphs 26-27). Although a combination may be covered by the claim, it is not protected by the claim when applying the test set out in *Gilead (*see paragraphs 28-30*):*

> *"26. I therefore accept that the effect of the word "comprises" is that claim 19 on its true construction covers products which include substances other than the compounds of claims 1-11 and 14. These may include an excipient, but they may also include another compound with anthelmintic activity. This conclusion is supported by the use of the wording "an active ingredient".*
>
> *27. I do not accept that it follows that claim 19 discloses a combination of a compound of claims 1-11 and 14 with another compound with anthelmintic activity. A claim may cover a product without disclosing it: see A.C. Edwards Ltd v Acme Signs & Displays Ltd [1992] RPC 131*
>
> *28. Accordingly, I accept that Profender is covered by claim 19. If one asks oneself what brings Profender within the scope of claim 19, however, it is clear that it is the presence of the empodepside. It is not the presence of the praziquantel, any more than it is the presence of the BHA.*
>
> *29. Applying the test articulated by Kitchin J in Gilead at [33], namely "to identify the active ingredients which are relevant to a consideration of whether the product falls within the scope of a claim of the basic patent", I consider that the answer in the present case is that it is only empodepside which is relevant. Accordingly, Profender is not protected by claim 19 of the Basic Patent within the meaning of Article 3(a) of the Regulation as interpreted in Gilead.*
>
> *30. To put the same point another way, the present case is to be distinguished from Gilead. In that case the basic patent specifically disclosed and claimed a combination of active ingredients, whereas in this case the Basic Patent does not.*"

61 Arnold J also considered an alternative position that if no SPC could be granted for a combination of active ingredients then the applicant was entitled to an SPC for a single

active. However he found that the applicant was not entitled to such a certificate stating in paragraph 48:

> *"An application for such an SPC would not comply with Article 3(b) of the Regulation since Astellas has not been granted a marketing authorisation for emodepside as opposed to Profender: see the recent decision of the Court of Appeal in Generics (UK) Ltd v Daiichi Pharmaceutical Co Ltd [2009] EWCA Civ 646, in particular at [57]-[58]."*

62 In *Centocor Inc' s SPC application*[18]*,* the hearing officer found that an SPC could not be granted under Article 3(a) for the product Centoxin, HA-1A human monoclonal antibody, on the basis of a basic patent which protected the combination of a monoclonal antibody and an anti-microbial agent. The applicant considered that the basic patent protected the antibody, i.e., product for which the SPC was being sought, by virtue of infringement under Article 60(2) of the Patents Act 1977, i.e. by applying an infringement test. The hearing officer did not agree and found that even if there are circumstances in which supply of the antibody on its own was an infringing act with regard to section 60(2), it did not follow that the antibody on its own was protected by the basic patent for the combination. This is consistent with the decisions of the Court in both *Gilead* and *Takeda* and the interpretation of the Regulation in these decisions that infringement of a patent is not necessarily the same as protection.

Analysis & Argument

63 In order to determine if, as is required under Article 3(a) of the Regulation, the product which is the subject of this SPC application is protected by the basic patent in force, I must analyse carefully the claims in the basic patent alleged to protect the product.

Basic Patent EP 0667165 B1

64 The basic patent concerns the preparation and use of monoclonal antibodies which are specific to a human receptor for epidermal growth factor (EGF) which can inhibit the growth of human tumour cells that express human EGF receptors in conjunction with anti-neoplastic agents to treat cancer. The patent describes how to make these monoclonal antibodies, the anti-tumour activity of the antibodies on their own and the anti-tumour activity of the antibodies in combination with neoplastic agents.

65 The claims of relevance to this decision are claim 1 and claim 2 which read:

> "1. A therapeutic composition comprising:
>
> (a) a monoclonal antibody which inhibits the growth of human tumor cells by said antibody binding to the extra-cellular domain of the human EGF receptors of said tumor cells in an antigen-antibody complex, said tumor cells being characterized by their expression of human EGF receptors and mitogenic stimulation by human EGF, and
>
> (b) an anti-neoplastic agent;

[18] see [1998] RPC 118

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

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

66 The description, for example at paragraphs [0012]-[0014] and [0018] indicates that the monoclonal antibodies described which have specific binding properties to the receptor for epidermal growth factor (EGF) in humans have a cytostatic effect i.e. they halt cell replication, but they do not have any cytotoxic properties, i.e. ability to destroy cancer cells. Anti-neoplastic agents, such as cisplatin and doxorubicin, are effective cytotoxic agents but when used on their own are effective only at levels which have serious side-effects for the patient. By using an EGF-receptor specific monoclonal antibody, such as cetuximab, in combination with an anti-neoplastic agent, such as cisplatin or doxorubicin, it has been found by the applicant that a significantly lower amount of the anti-neoplastic agent is required to achieve a therapeutic effect. Various anti-neoplastic agents that can be used in combination with EGF-receptor specific monoclonal antibodies to treat cancer effectively are listed in para [0018] and examples of such combinations are provided in paras [0065] and [0066]. Both agents appear to act through different mechanisms to exert their therapeutic effect but, as the description makes clear, the combined treatment, i.e., antibody with anti-neoplastic agent, is more effective than each of the treatments on their own, i.e. antibody on its own or anti-neoplastic agent on its own (see para [0066] and Figures 9-11). Claim 2 indicates that a composition comprising the anti-neoplastic agent and the antibody may be such that each component is given separately to the patient rather than combined in a single dose.

67 Thus, it is clear whether administered together or separately, the use of both components together is more effective than the use of either component on its own. The innovation that the patent has been granted for is thus the preparation and therapeutic use of an antibody, such as cetuximab, which binds specifically to EGF receptors in human cells, with an anti-neoplastic agent, such as irinotecan. There is nothing, in my view, in the disclosure of the patent to indicate that it was envisaged to use the antibody on its own. Indeed it is clear that the antibody on its own is not effective in reducing tumour growth only in halting it (see para [0012]). As a consequence, I agree with the assessment of the examiner that this patent is not suitable as the basic patent in support of SPC application SPC/GB 04/038 which specifies cetuximab only as the product. However, as indicated above, it is suitable as the basic patent in support of SPC application SPC/GB 04/037, which specifies cetuximab and irinotecan as the product.

68 Mr Powell indicated at the hearing that his argument in support of this application was based on an infringement argument. In summary, this was if one was to make an antibody such as cetuximab, which binds to human EGF-receptors, available for the purpose of using it or including it in a combination with irinotecan or another anti-neoplastic agent as claimed in patent EP 0667165, this would amount to an infringement under Section 60 of the Patents Act 1977. Thus the patent protects the product cetuximab and, for the purposes of Article 3(a) of the SPC regulation, the product as claimed in this SPC application would be protected by a basic patent in

force. He maintained, when questioned, that in the context of this application the MA was not for the medicinal product Erbutix comprising cetuximab as the active ingredient but rather was only for the combined product of cetuximab with irinotecan. Thus an antibody such as cetuximab could only be made available for use in humans in a product which combined it with an anti-neoplastic agent.

69 Mr Powell acknowledged that such an infringement argument had been rejected by the court in *Takeda* (see above) and that, while Kitchen J in *Gilead* and Arnold J in *Astellas* had recognised that there were some outstanding issues with *Takeda*, he accepted that the Office as a lower tribunal was bound by the decisions of the higher court.

70 In *Astellas*, Arnold J made clear that he considered there was a distinction between the scope of protection provided by the patent, and any subsequent SPC, and the question of infringement – the scope of protection is limited to that specified in the claims properly construed. Despite his acknowledgement that not all issues in relation to the infringement test had been considered in *Takeda* and that a higher court might want to consider them, for example, did the decision of the ECJ in *Farmitalia*[17] actually endorse or reject the infringement test; Arnold J did not consider that *Takeda* was wrong. Thus, as the hearing officer in the lower tribunal, I remain bound by this decision. Thus, I do not consider that the basic patent protects the product cetuximab on its own.

71 I find support for my view in the Office decision on *Centocor Inc's SPC Application*[19]. In this case, the basic patent claimed a product comprising a monoclonal antibody and an anti-microbial agent in a combined preparation but the product licence (i.e., MA) only referred to Centoxin (HA-1A human monoclonal antibody), i.e., the monoclonal antibody on its own. The hearing officer found that a reference in the MA to the fact that the antibody could be used "along with the appropriate antibiotics and supportive therapy" to treat sepsis syndrome, i.e., septic shock was not sufficient to make this MA a valid authorisation for a combination of the antibody with an anti-antimicrobial agent, but rather it suggested that the anti-microbial agent is administered separately from the antibody. The basic patent did not envisage the use of the antibody and the anti-microbial agent in anything other than a combined preparation. Although, in the present case, the basic patent, does envisage the separate administration of the monoclonal antibody and the anti-neoplastic agent, this is not the same as saying that it envisages the use of the antibody cetuximab on its own without the anti-neoplastic agent. The innovation protected by the patent cannot be achieved without the use of an anti-neoplastic agent as well as the antibody.

72 Mr Powell went on to argue that he considered that the present situation was an example of the kind of harsh result that Kitchen J had in mind in paragraphs 23-30 of *Gilead* and that the applicant was in real danger of not receiving any SPC at all.

73 I consider that the present situation is different to that in *Gilead*. The product being claimed here in this SPC application is cetuximab on its own and it relies on a basic patent which only protects a combination of cetuximab with irinotecan. Mr Powell indicated that this application could be considered as the mirror image of the situation in *Takeda* and *Gilead*. In the latter cases, a SPC was being sought for a narrower monopoly, a combination, than was provided by the basic patent which covered one of

[19] see [1996] RPC 118

the components in the combination claimed. In the present case, the SPC is being sought for a single component in the combination. The latter is clearly a wider monopoly than that claimed in the basic patent as it would include that component on its own or in combination with others. Mr Powell argues that the MA only authorised the combined product cetuximab and irinotecan when the application was made. Thus granting an SPC for cetuximab will only protect the combination as this is all that had been authorised. I disagree with this view for the reasons I have indicated above in relation to SPC application SPC/GB 04/037 because I consider that the MA authorised the medicinal product Erbutix comprising the product cetuximab and not the combination of Erbutix and Irinotecan. Also, a granted SPC for cetuximab would include any further uses authorised for this product following this first authorisation. On this basis, granting an SPC for the product cetuximab would be granting a wider monopoly than was protected by the basic patent.

Conclusion

74 Taking account of all of the above, I conclude that European marketing authorisation EU/1/04/28/1/001 for "Erbutix-cetuximab" is not, for the purposes of Article 3(b) of the Regulation, a valid authorisation to place the product, "cetuximab in combination with irinotecan", which is the subject of application SPC/GB/04/037, on the market as a medicinal product.

75 Also, I conclude that, for the purposes of Article 3(a) of the Regulation, the basic patent EP 0667165 B1 does not protect the product "cetuximab" which is the subject of SPC application SPC/GB 04/038.

76 Since in accordance with Article 10(3) of the Regulation, an opportunity to correct the irregularities in these applications has been given, as required by Article 10(4), I reject both these applications.

Appeal

77 Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days.

Dr L Cullen
Deputy Director acting for the Comptroller