

## **SPCs covering combination products – current validity issues across Europe?**

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### **Introduction**

Also posted today on the EPLAW Patent Blog is an article by Philippe de Jong, who discusses the scope of protection of Supplementary Protection Certificated (“SPCs”). One of the issues addressed by de Jong is the scope of protection of SPCs in case of combination products, i.e. medicinal products consisting of two (or more) active ingredients.

This article aims to address the validity of SPCs covering combination products. In particular, the question is addressed how the requirement of article 3 sub a of Regulation 469/2009 concerning the supplementary protection certificate for medicinal products (“the SPC-Regulation”), i.e. that the product for which SPC protection is sought, must be protected by a basic patent in force.

First, the general background of SPCs covering combination products will be sketched, including a discussion the relevant legal framework and some recent case law. Then, some of the issues at stake will be reviewed by reference to a recent case (cetuximab), to conclude with a number of comments and hopefully practical tips for getting the most out of your future SPC applications.

### **The law**

The SPC-Regulation creates a European system for the extension of patent terms for medicinal products for which a marketing authorisation has been obtained. The idea behind the granting of SPC’s is to compensate the innovative pharmaceutical industry for the often time consuming marketing authorization procedure by offering a maximum of five years extended protection for a new medicament.

Article 1 of the SPC-Regulation defines a *product* to mean the active ingredient or combination of active ingredients of a medicinal product. The *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.

Article 3 stipulates the conditions for obtaining a certificate. There are four basic requirements:

- (a) the product is protected by a basic patent in force;
- (b) a valid authorization to place the product on the market as a medicinal product has been granted;
- (c) the product has not already been the subject of a certificate;

(d) the authorization referred to in (b) is the first authorization to place the product on the market as a medicinal product.

Article 4 defines the scope of protection of an SPC as follows: "Within the limits of the protection conferred by the basic patent, the protection conferred by a certificate shall extend only to the product covered by the authorization to place the corresponding medicinal product on the market and for any use of the product as a medicinal product that has been authorized before the expiry of the certificate."

### Recent cases

There have been a number of important decisions of national courts<sup>1</sup>, notably also the High Court in London, relating to SPCs for combination products. Essentially, two situations can be distinguished i) the marketing authorisation ("MA") has been obtained for a combination of active ingredients *as such* and the basic patent designated for purposes of obtaining an SPC claims only one of the actives. In situation ii) the MA relates to a single active ingredient, whereby the product is in practice marketed for use in a combination therapy and is claimed as such in the basic patent.

#### UK

In the *Takeda*<sup>2</sup> case the basic patent covered the antibiotic lansoprazole, and an SPC was sought for the combination of lansoprazole and another active ingredient. On appeal, it was held that the combination of lansoprazole and the other active ingredient only infringed the basic patent because of the presence of lansoprazole and that therefore the combination was not protected by the basic patent. (Then) Mr. Justice Jacob held:

"The SPC system is to provide supplementary protection to that provided by the patent—to extend the relevant part of the patent monopoly. It is not a system for providing protection for different monopolies. Here, Takeda's monopoly is in lansoprazole. The monopoly which they seek is a combination of lansoprazole and an antibiotic. The fact that combination might infringe the monopoly given by the patent simply because one component infringes is irrelevant."<sup>3</sup>

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<sup>1</sup> Although the SPC-Regulation is "true" unitary European Union law, national authorities (often patent offices) are appointed to grant SPCs. Appeals from the rejection of SPCs are dealt with by national courts. Also, the validity of SPCs can become an issue in the (private law) enforcement of and SPC. It must be noted, however, that the ECJ has the final say in legal issues relating to SPCs.

<sup>2</sup> Takeda Chemical Industries Ltd's SPC Applications (No 3) [2004] RPC 1

<sup>3</sup> This decision followed and referred to an earlier Swedish case, wherein A/B Hassle tried to obtain an SPC for a combination of two active ingredients, whereby only one of these was covered by the basic patent. The Swedish Patent Office, the Patent Appeal Court and the Supreme Administrative Court all came to the conclusion that there was no compliance with Art.3(a). (Case number 3248-1996).

In *Gilead*<sup>4</sup>, the MA was granted for a product comprising, as its active ingredients, tenofovir and another antiretroviral. The basic patent covered a class of new antiretroviral compounds useful in the treatment of HIV, including tenofovir. Gilead sought SPC protection for the combination product. Following *Takeda*, the UK patent office held that not everything that infringes can be said to be “protected by a basic patent”, thus rejecting the so-called “*infringement test*”.

On appeal, Kitchin J did not give a definitive ruling on the applicability of the infringement test and concluded that this ought to be decided by a higher Court (i.e. the Court of Justice of the European Union). In particular, he noted that:

“the Takeda test [may] produce a harsh result. For example, the holder of a patent for a new pharmaceutical may have chosen to market it only in combination with another active ingredient and duly secured a marketing authorisation for the medicinal product containing those ingredients. In such a case the product would appear to be the combination of active ingredients (Article 1(b)) for which authorisation has been obtained (Article 3(b)). Yet, upon an application of the Takeda test, it would not be protected by the basic patent and hence the inventor would be deprived of an opportunity to secure any SPC at all.”

On the other hand, the drawback of the infringement test according to Kitchin J would be:

“that the holder of a basic patent could first obtain an SPC for the active ingredient the subject of the patent, so giving him perhaps one or two years of protection beyond the life of the patent, and then, some years later, obtain another SPC for a combination of the same ingredient together with another active ingredient and so gain protection for a full five years beyond the life of the patent.”

In the end, the case was decided in favour of Gilead since according to Kitchin, the combination was specifically disclosed in one of the subclaims. In doing so, Kitchin J introduced another test, which involves *identifying* “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.”

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<sup>4</sup> Gilead Sciences Inc.'s SPC Application [2008] EWHC 1902.

*Astellas*<sup>5</sup> related to a application for a product containing two active ingredients, only one of which was disclosed and claimed in the basic patent. In accordance with *Gilead*, Arnold J found that the product was not protected by the basic patent. With regard to the applicability of the infringement test he held:

“I am not convinced that Takeda is wrong. To my mind, Jacob J's reasoning remains persuasive. Furthermore, I agree that there is a distinction between the scope of protection and the question of infringement. As to *Farmitalia*, it is not clear to me that the ECJ either endorsed or rejected the infringement test in that case. Nevertheless, I agree with Kitchin J that there are arguments in favour of the infringement test which do not appear to have been considered in *Takeda* and which merit consideration by a higher court and perhaps the ECJ.”

Arnold J went on to apply the “identify the relevant active ingredients”-test from *Gilead* and concluded that the combination was not “protected by a basic patent” in the sense of the SPC-Regulation. As to the final word on the applicability of the infringement test, also Arnold J considered that this would be a matter to be decided by a higher court.

The same line of reasoning was once again followed in the recent *Medeva*<sup>6</sup> case, relating to vaccines containing up to nine antigens whereby the basic patent only disclosed two. Kitchin J reiterated his *Gilead* test and decided that the basic patent did not protect the combination of nine active ingredients.

#### The Netherlands

It seems as if the Dutch courts use a similar test as adopted by the UK courts in assessing whether or not an active ingredient is covered by the basic patent designated by the patentee. The test applied by the Dutch courts appears to have certain elements in common with the infringement test, but seems to exclude anything going beyond anything that is claimed *as such* in the basic patent.<sup>7</sup>

The Patents Court of Appeal explained what it considers the proper test as follows<sup>8</sup>:

“This question [i.e. the question whether a product is “protected by a basic patent” in the sense of the SPC-Regulation, AK] differs substantially from the question whether there would have been a

<sup>5</sup> *Astellas Pharma Inc.'s SPC Application [2009] EWHC*.

<sup>6</sup> *Medeva BV v The Comptroller General of Patents [2010] EWHC 68*.

<sup>7</sup> See, however, the Hague District Court, 12 October 2005 *B9 1039 (Sankyo v. Merial)*, which equates the question whether a product is “protected by” the basic patent to an assessment of the scope of protection of the basic patent and whether or not the product falls within said scope.

<sup>8</sup> The Hague Court of Appeal, 21 February 2008, *Ranbaxy v Warner-Lambert re SPC Atorvastatine, IEPT20080221*.

patent infringement [...] In establishing infringement, the court must determine the scope of protection of the patent in accordance with article 69 EPC and the accompanying Protocol for its interpretation. Thereby, the court is not confined to answering the question of [...] literal infringement, but may, if necessary, [...] consider] infringement by way of equivalence. According to the Court of Appeal Ranbaxy was hence right in stating that to answer the question whether or not an SPC has been rightfully granted by the Dutch PO based on the [invoked patent] the doctrine of equivalence should not play a role. In this regard also see e.g. T 0442/91...[]. The questions which have to be addressed [] by the PO for the granting of an SPC are, in sum, for which new and inventive subject matter has the EPO granted exclusive rights and does that subject matter relate to the product mentioned in the marketing authorisation?”.

In other words, one has to determine the subject matter of the claims and then has to assess whether the product *relates to* the claimed subject matter. This is not an infringement test, as has been expressly stated by the Court of Appeal, but rather seems to resemble the UK “identification test”. If the product as such, i.e. the specific combination or, as in the Dutch *lipitor* case the enantiomer, can be identified in the subject matter of the invention as defined by the claims, the product is deemed to be *protected by* the basic patent.

#### Germany

In Germany, the situation seems different than in the UK and the Netherlands, where – at least so far – the infringement test has been rejected. Following the Federal Supreme Court decision in *Pantoprazole*<sup>9</sup>, the German courts do apply the infringement test to assess the validity of SPCs in light of the requirement of article 3 sub a of the SPC-Regulation. In this case, the marketing authorisation was granted for pantoprazole (a proton pump inhibitor) as a single active ingredient, but as a further indication, the marketing authorisation mentioned the use in combination with an anti-helicobacter agent. The basic patent designated by the patentee for purposes of obtaining an SPC claimed only the combination of both active substances. The Federal Supreme Court was fairly straightforward in its argumentation and held that by definition a single substance cannot infringe upon a combination claim. As a consequence, the SPC was denied.

On basis of the decision in *Pantoprazole*, it can be concluded that the German courts do in fact apply the infringement test to determine whether a product is protected by a basic patent in the sense of the SPC-Regulation. Also, arguments based on the doctrine of equivalence may be taken

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<sup>9</sup> Federal Supreme Court, 8 July 2008, "Anti-helicobacter preparation", FSC X ZB 1/08.

in to account, just as in “real” cases of infringement.<sup>10</sup> It seems however that the infringement test applied by the Federal Supreme Court is limited to the assessment of *direct* infringement.

The European Union member states also have provisions that cover *indirect* (or contributory) infringement. Indirect infringement relates to the situation in which someone markets means that are essential for the patented invention. In the case of a combination patent, it may be that – under circumstances – marketing one of the two (or more) active substances amounts to indirect infringement. In the first instance decision in the *Pantoprazole* case<sup>11</sup>, a similar argument was forwarded in that by mentioning the combination as an indication in the MA, the MA actually extended to the combination. This argument was rejected by the Federal Patents Court and was no longer an issue during the appeal. It is thus noted here that although the German courts apply the infringement test, this does not extend to cases of indirect infringement.

Now, by reference to the recent *cetuximab* case, it will be discussed how refusal of the Dutch and UK Courts to apply the infringement test and, more in particular, also not applying the indirect infringement test, plays out in practice.

### **The cetuximab case**

In the cetuximab case, the marketing authorisation was granted for the product cetuximab, a monoclonal antibody. The MA mentioned the use of cetuximab in combination with irinotecan for treatment of patients with certain types of cancer. Although the MA did thus specifically mention the combination, it was not confined to such combination. It could be said that the mention of the combination treatment was directed towards doctors, rather than an actual limitation of the MA itself. For the sake of the argument (and conciseness) it is accepted here that the cetuximab MA covers the product cetuximab consisting of one single active ingredient.<sup>12</sup>

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<sup>10</sup> See Federal Patent Court 16 June 2009, *Arelis*.

<sup>11</sup> Federal Patent Court, 23 November 2007, "Anti-helicobacter preparation".

<sup>12</sup> The SPC applicants had argued extensively that the MA (and consequently the product) was actually for a combination of active ingredients, because this would bypass the problem discussed here, i.e. a patent for a combination product as 'basic patent' for a single ingredient. The UK hearing officer – similar to the Dutch courts – held that:

“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 Erbitux. [...] 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.”

SPC-protection was sought for the product cetuximab. The basic patent designated by the patentee for this purpose claimed:

*“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;*

*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.”*

SPCs were refused by the Dutch PO and the UK PO for similar reasons. Basically, both SPC granting authorities held that the single product could not be identified *as such* in the basic patent. The UK hearing officer said:

“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.”

The applicant appealed the refusal by the PO to grant an SPC for the product cetuximab. The Council of State [the highest Dutch administrative court] followed the Dutch PO (just as the District Court of The Hague did)<sup>13</sup> and held that the DPO was right in not granting an SPC because the product *does not fall within the scope of protection of the basic patent at all times*.<sup>14</sup> Again, the court

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<sup>13</sup> District court of The Hague 28 May 2009, *JGR 2008/32*.

<sup>14</sup> Par. 2.4.1. To the extent that there seems to be light between the Court of Appeal “relates to the claimed subject matter”-test and the Council of State “protection at all times”-test, this may be explained by the fact that these are separate courts which are not bound to each others interpretations. The Court of Appeal deals with appeals of private law (patent enforcement) cases, whereas the Council of State deals with appeals in administrative law cases, such as the refusal to grant an SPC by the Dutch Patent Office. From a substantive

here refuses to apply the infringement test, but rather assesses whether the product as such is covered by the claims of the basic patent designated.

Although it is true that an SPC is a right in itself, with its own granting criteria and its own scope of protection, the cetuximab case shows that too narrow a construction of the SPC-Regulation, such as the Dutch (and UK) courts seem to have applied may lead to unfair results. In cetuximab, the courts refused to grant SPCs for a single product on basis of a combination patent. It is argued below that the system of the SPC-Regulation offers sufficient safeguards to prevent “ever greening” and overly broad SPCs.

### **Comment to cetuximab**

On the outset, it should be noted again that the ratio of the SPC system is to compensate for the mandatory marketing authorization procedure, which reduces the effective monopoly time afforded by a patent, by extending protection for a maximum of five years. This ratio explains why for the granting of an SPC on the one hand there has to be an existing basic patent and on the other hand there is the concept of a “product”. After all, there has to be a genuine technological contribution that is embodied in a product for which a marketing authorization procedure has been followed. The fact that the term “product” in article 1 sub b of the SPC-Regulation has to be interpreted narrowly, is evidenced by a series of rulings of the European Court of Justice<sup>15</sup>. This makes sense because in the alternative more certificates could be granted for the same medicinal product. However, for an unduly strict interpretation of the term “protected by a basic patent”, as the Dutch and UK Courts seem to be applying, there seems to be no good ground. After all, to the extent that there is a product in the sense of the SPC-Regulation, which is covered by any “valid” patent, there has been an innovation that deserves supplementary protection.

The substantive legal question whether a product is protected by a basic patent, is a matter of national law, such is known from *Farmitalia*<sup>16</sup>. The exact scope of that protection is yet a further question. This follows from the system of article 4 in conjunction with article 1 sub c of the SPC-Regulation. The basic patent may according to article 1 sub c be a product or method patent, but may also be a patent for the “application of a product” (meaning: a (second) medical indication or use). It is a condition that the basic patent is explicitly identified by the patentee with a view of obtaining the certificate. Article 4 makes clear that the protection conferred by a certificate shall

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legal perspective, however, this author is of the opinion that there is little difference in outcome between the two tests applied.

<sup>15</sup> In particular ECJ 4 May 2006, case 431/04 (*Massachusetts Institute of Technology*), ECJ 17 April 2007, case C-202/05 (*Yissum*).

<sup>16</sup> ECJ 16 September 1999, case C-392/97 (*Farmitalia*).

extend only to the product *within the limits of the protection conferred by the basic patent*. This provision ensures that the protection conferred is proportional to the extent of the technological innovation.

For the product cetuximab a marketing authorization had been obtained and this was the first marketing authorization for the medicinal product cetuximab. Hence, the product-requirement is met. The authorization, however, covers (at least in theory) more than the basic patent. The marketing authorization is valid for the product cetuximab *per se* while the patent only protects the narrower combination of cetuximab and another medicinal product. Therefore the product cetuximab in itself does not directly infringe the patent. There may be indirect (or contributory) patent infringement, in case cetuximab would be offered with a view of applying it in combination with the other medicinal product and it is to be regarded as “means regarding an essential part of the invention”<sup>17</sup>.

In essence, this situation is not different from the situation in which there is an SPC for a product that is protected by a basic patent for a (second) medical use. The patent for the combination of cetuximab and the other medicinal product could just as well be read as “*use of cetuximab for the treatment of patients with cancer who are also being treated with other medicinal product*”. This type of claim is explicitly allowed by the SPC-Regulation. Whether there is direct or indirect patent infringement, this shows, is not a relevant criteria. After all, a product by itself can never directly infringe a patent for a second medical use. There can only be infringement if the product is intended for the claimed use<sup>18</sup>. In such a situation there is by definition indirect (or contributory) infringement.

From the MIT- and Yissum rulings<sup>19</sup> of the Court of Justice we have learned that the term “product” in the regulation should be construed narrowly and that the second medical indication may not be used to define the product in the sense of the SPC-Regulation. This makes sense, because if that were to be allowed, the same product could enjoy supplementary projection twice simply because the medical indication is amended. Vice versa, the basic patent may of course exclusively protect a (novel) medical use – this follows unambiguously from the SPC-Regulation itself. In that case also, the product in the sense of the SPC-Regulation is not covered in *all* circumstances by the patent. For instance, it may be possible to use the product for another, non-patented use, without there being an infringement. This would not constitute an infringement of the patent and *therefore* not of the certificate (see article 4 of the SPC-Regulation). At the same time, this goes to show that the

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<sup>17</sup> See for instance art. 73 (1) DPA 1995. In my opinion there are good grounds to argue that in the case of a patent for combination product both ingredients are “means regarding an essential part of the invention”.

<sup>18</sup> Protection for (second) medical uses is also referred to as “product insert protection”.

<sup>19</sup> ECJ 4 May 2006, case C-431/04 (*Massachusetts Institute of Technology*), ECJ 17 April 2007, case C-202/05 (*Yissum*).

“identification test” is not the proper one, for one might argue that in a use-claim as mentioned above, the product in question could be identified contrary to in a combination product claim.

In case the product is only protected in some cases by the basic patent (like here, only if there is an intended use in combination with another medicinal product), this author would defend the position that the SPC ought to be held valid, in which case the scope of protection of the SPC would be significantly narrowed. This is for the patentee to decide. It is a pity that the Dutch and English courts seem to decide otherwise so resolutely, maybe because of the facts of the case and the positions of the parties. Perhaps at least to be on the safe side, they could have posed questions to the Court of Justice.

### **Conclusions - what to do?**

There have been quite a number of recent developments in European SPC cases relating to combination products. Courts seem to have difficulties in dealing with this issue and various tests have been developed by different national courts. Notably, the UK and the Netherlands seem to be closest together in applying the “identification”-test and “product relates to claimed subject matter”<sup>20</sup>-test, respectively. In Germany, an infringement test is applied including infringement by equivalence, however, with the exception of indirect infringement. As exemplified by the recent cetuximab case, it was argued here that there should be a liberal (infringement, including indirect infringement) test for determining whether a product for which SPC protection is sought is protected by a basic patent in terms of the SPC-Regulation. The latter comprises enough safeguards to ensure a fair protection for the patentee taking into account the interests of third parties. In the end, the final word is and should be to the Court of Justice of the European Union.

For now, practitioners in Europe are once again stuck with different legal situations in different Member States. Nevertheless, a common denominator seems to be that courts are inclined to give a strict, narrow rather than a broad, liberal construction of the requirement “protected by a basic patent” in the SPC-Regulation, in fact contrary to the position taken by this author. Therefore, to be on the safe side, it may be advisable for patent drafters to already at an early stage give due consideration to potential combination therapies, which preferably should be expressly claimed. On the other hand, if it is known at an early stage that a product is intended to be marketed as a combination therapy and especially if the basic patent already claims this, it may be advisable for patent attorneys to liaise with the regulatory department to consider applying for marketing authorisation as a combination product.

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<sup>20</sup> Product must be protected by the basic patent *at all times* according to the Council of State in the cetuximab case,

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