VACCINES AND SPCs: THE CJEU REACHES A FORK IN THE ROAD

SIMON COHEN AND PAUL ENGLAND*
Taylor Wessing Patents Group, London

Introduction: The Challenge Posed by Vaccines

In the latest of many references that he has made to the Court of Justice of the European Union (CJEU) on the subject of supplementary protection certificates (SPCs), Arnold J recently said this:

I would observe that this is the third time in six months that I have had to refer questions of interpretation of the SPC Regulation to the CJEU. I do so with considerable regret. That this should be necessary demonstrates the dysfunctional state of the SPC system at present. This is primarily due to the poor drafting of the SPC Regulation and to the failure of the European Commission, Council and Parliament to revise it to address the problems which have emerged. Matters have not been assisted, however, by the fact that the Court of Justice's recent case law interpreting the SPC Regulation has not provided the level of clarity and consistency that is required.

What is the source of this – by judicial standards – outspoken frustration with the SPC Regulation? It is another case in which the court is struggling to apply the provisions of the SPC Regulation to a vaccine product, GlaxoSmithKline v Comptroller-General of Patents. Why should vaccines pose a problem to the scheme of additional protection afforded by an SPC? The basis of the problem is described in a case actually concerned with an SPC for a second medical use product rather than a vaccine, Neurim. In this case, Jacob LJ makes this observation:

28 We consider that Neurim's arguments [for SPC protection] are not only tenable: in our view they are right. Many kinds of valuable pharmaceutical research will not get the encouragement or reward they deserve if they are not [capable of SPC protection]. Pharmaceutical research is not confined to looking for new active compounds. New formulations of old active substances are often sought. Most are unpatentable but from time to time a real invention is made and patented.

30 In short, if Neurim are wrong, then the Regulation will not have achieved its key objects for large areas of pharmaceutical research: it will not be fit for purpose. Whether that is so or not is clearly a matter for the EU's highest court.

The problem identified by Jacob LJ in the context of second medical use applies similarly to vaccines: the SPC Regulation was drafted on the assumption that the products to which it will apply are small molecule compounds – ‘new active compounds’. Attempting to seek SPC protection for a product that falls outside that simple model stretches beyond the framework of the SPC Regulation. This is a problem because, as Jacob LJ says, the consequence is that the SPC Regulation fails to protect products emerging from other areas of very substantial pharmaceutical research and investment.

Vaccines fall outside the simple model. The simplest description of a vaccine is that it is any preparation intended to produce immunity to a disease by stimulating the production of antibodies. They can include, for example, suspensions of killed or attenuated microorganisms, or products or derivatives of microorganisms, and the more recent application of sophisticated molecular biology techniques has allowed the production of vaccines comprising pure, recombinant polypeptide/protein sequences.
More significantly, as regards the application of the SPC Regulation, there are two particular characteristics of treatment with vaccines that cause complications. These are associated with their delivery to patients as therapeutic products:

1. Combination vaccines: the European Medicines Agency (EMA) Working Party on Vaccinations has observed that vaccination schedules, particularly the crowded schedules applied during infancy that commonly require concomitant administrations of two or more vaccines, are becoming increasingly complex. This has focused attention on the need for co-administration of vaccines (that is, the administration of more than one vaccine at the same visit to a healthcare facility). In many instances, this militates towards co-administration by use of combination vaccines containing multiple antigens, perhaps with other monovalent vaccines or other combination vaccines, or both; and

2. Adjuvants: components in vaccine formulations aimed at enhancing, accelerating and prolonging the specific immune response desired from a vaccine. The EMA sets out several of the advantages of using adjuvants:

(a) the enhancement of the immunogenicity of antigens;
(b) modification of the nature of the immune response;
(c) the reduction of the antigen amount needed for a successful immunisation;
(d) the reduction of the frequency of booster immunisations needed; and
(e) an improved immune response in elderly and immuno-compromised vaccinees.

The interest in applying adjuvants in vaccines, although nothing new, has been growing. In particular, public health authorities, such as the World Health Organisation (WHO), have set goals for enhancing the efficacy of existing vaccines as well as for developing new ones. Indeed, although many new vaccine candidates have appeared for infectious diseases, allergic and autoimmune diseases, and cancer and fertility treatment, many require adjuvants to enforce their efficacy because of their low immunogenicity. Furthermore, the provision of effective adjuvants has been assisted by developments in technology and immunology, allowing better adjuvant development and application.

It is this issue of combinations in therapeutic products, as well as the use of adjuvants, that has provided a particular and ongoing challenge to the SPC Regulation. The way in which it has done so, as explained below, is surprisingly complex.

This article explains the main issues applicable to vaccines that have been addressed by the CJEU, further problems that have arisen as a result of the CJEU’s decisions, and where the ‘dysfunctional’ state of the system currently leaves SPC protection for these important therapies.

**SPC Protection for Combinations**

**The Vaccine Applicant’s Dilemma**

Assume that a vaccine A is to be marketed and administered together with one or more other vaccines in a combined product (A+B+C). In the SPC context, this scenario has raised particular difficulties of interpretation under SPC Regulation Articles 3(a) and 3(b) (as supplemented by Article 3(d)). Article 3 states:

**Article 3**

**Conditions for obtaining a certificate**

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.

The important questions that arise for combination products under this Article are whether a marketing authorisation (‘MA’) for product A+B+C is capable of constituting a ‘valid authorisation’ of product A alone, for the purposes of Article 3(b). Or can it only serve as an authorisation for A+B+C? The answer to this question matters, because an applicant who seeks an SPC on product A, based on a patent covering product A, but who must market A in combination with B and C, must rely on a first authorisation for A+B+C, rather than A alone.

As an alternative, an applicant might seek an SPC to protect product A+B+C, so that its SPC application reflects the MA instead of the patent. The requirements of Article 3(b) would certainly be satisfied because the MA covers A+B+C. However, in this situation, is the patent covering A alone a ‘basic patent protecting’ the combination product A+B+C for the purpose of Article 3(a)?

Clearly, if the answer to both of the questions (see Table 1) is ‘no’, the applicant for an SPC on a product authorised as a combination vaccine is caught on the horns of a dilemma between Article 3(a) and 3(b) of the SPC Regulation. As a consequence, a number of references have been made to the CJEU from national courts seeking guidance on how to apply the SPC Regulation in these circumstances, the concern being that it may not be possible to obtain an SPC in these circumstances at all. The results of these references are discussed below, beginning with Article 3(b).

**Table 1: The SPC applicant’s dilemma**

<table>
<thead>
<tr>
<th>Patent</th>
<th>MA</th>
<th>SPC</th>
<th>Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A+B+C</td>
<td>A</td>
<td>Is the MA for A+B+C a valid authorisation for an SPC on product A, further to Article 3(b) SPC Regulation?</td>
</tr>
<tr>
<td>A</td>
<td>A+B+C</td>
<td>A+B+C</td>
<td>Is product A+B+C protected by a patent for A alone, further to Article 3(a) SPC Regulation?</td>
</tr>
</tbody>
</table>

**Article 3(b): Valid Authorisations for Combination Products**

Is the MA for product A+B+C capable of constituting a ‘valid authorisation’ of product A alone for the purposes of SPC protection under Article 3(b)? This question arose in the context of the fifth SPC application in Medeva BV’s SPC Applications.9

The Medeva case concerned an application by Medeva for five SPCs with the UK Intellectual Property Office (‘UKIPO’), seeking protection for permutations of combined vaccines against diphtheria, tetanus, whooping cough, poliomyelitis and/or meningitis. In support of these applications, Medeva cited a number of French, German and UK MAs. These MAs had in common that they were for combinations of pertactin and filamentous haemagglutinin antigens, but each contained several other, varying, combinations of active ingredients (see Table 3). The European patent on which Medeva based its SPC applications was for a method of the preparation of an acellular vaccine against Bordetella pertussis (whooping cough agent). This vaccine as claimed consisted of a combination of two antigens as active ingredients: pertactin and filamentous

---

9) Medeva BV’s SPC Applications (Case C-322/10) [2012] RPC 25.
haemagglutinin; unlike the combinations for which the MAs were granted, there were no other antigens combined with these.

In the fifth application, the active components and ingredients identified in the patent mirrored those in the SPC application (a combination of pertactin and filamentous haemagglutinin). However, because the MAs authorised these antigens only in combination with other components, the UKIPO refused to grant the fifth application on the basis of Article 3(b). Medeva appealed this decision to the High Court and then to the Court of Appeal.

The Court of Appeal referred the following question to the CJEU, concerning Article 3(b):

6. Does … Article 3(b), permit the grant of [an SPC] for a single active ingredient or combination of active ingredients where:

(b) a medicinal product containing the single active ingredient or combination of active ingredients together with one or more other active ingredients is the subject of a valid authorisation granted in accordance with Directive 2001/83/EC or Directive 2001/82/EC which is the first marketing authorisation that places the single active ingredient or combination of active ingredients on the market?

The CJEU gave the following ruling on this question:10

Article 3(b) … must be interpreted as meaning that, provided the other requirements laid down in Article 3 are also met, that provision does not preclude the competent industrial property office of a Member State from granting a supplementary protection certificate for a combination of two active ingredients, corresponding to that specified in the wording of the claims of the basic patent relied on, where the medicinal product for which the marketing authorisation is submitted in support of the application for a special protection certificate contains not only that combination of the two active ingredients but also other active ingredients.

The consequence of this answer from the CJEU in Medeva is that the SPC need only be sought for one or more of the products for which the MA has been granted. In our example, therefore, an SPC can be sought for product A only, based on a marketing authorisation for A+B+C. In this case an SPC on pertactin and filamentous haemagglutinin antigens was permissible.

Article 3(a): Protection by a Basic Patent in Force

Does a patent for A protect the combination product A+B+C for the purpose of Article 3(a)? In Farmitalia,11 the CJEU had held that since patents were governed by national rules, based on the EPC, the extent of protection of a national patent for the purpose of Article 3(a) should be determined in accordance with those rules (that is, by the national courts). Subsequently, without any harmonised approach to guide them, the European national courts went very different ways. Some courts, such as those in Germany and the Netherlands, adopted a broad ‘infringement’ test. This asked whether the product in issue would in theory infringe the basic patent.12 If the product did infringe, then it would also be protected by the patent under Article 3(a).

According to the infringement approach, product A+B+C would be protected by a patent protecting A alone. Other courts – notably the French and English13 – had adopted variations of a narrower ‘subject-matter’ test, asking whether the product is part of the new and inventive subject-matter of the patent.

10) Re Medeva’s SPC Applications (Case C-322/10 and Georgetown University and others (Case C-422/10).
11) Farmitalia Carlo Erba SRL’s SPC Application (C-392/97).
12) See, for example, German Federal Supreme Court, ‘Anti-helicobacter preparation’, FSC X ZB1, 8 July 2008; and the District Court of The Hague, Meridia/Sankyo, B.I.E. 2007, 12 October 2005.
13) See, for example, Gilead Sciences, Inc’s SPC Application [2008] EWHC 1902 (Pat); and the Paris Court of Appeal in Daiichi Sankyo Company Limited v INPI, Case No. 09/065306, November 2009.
However, these varying approaches ultimately led to the English Court of Appeal also seeking guidance on the application of Article 3(a) in the Medeva case. In the remaining four of the five SPC applications made by Medeva, SPC protection was sought for combinations of more active components and ingredients than were covered by the claims of the patent. The Court of Appeal referred the following questions concerning Article 3(a) to the CJEU for a preliminary ruling:

(1) In the absence of Community harmonisation of patent law, what is meant in Article 3(a) ... by ‘the product is protected by a basic patent in force’ and what are the criteria for deciding this?

(2) In a case like the present one involving a medicinal product comprising more than one active ingredient, are there further or different criteria for determining whether or not ‘the product is protected by a basic patent’ according to Article 3(a) ... and, if so, what are those further or different criteria?

(3) In a case like the present one involving a multi-disease vaccine, are there further or different criteria for determining whether or not ‘the product is protected by a basic patent’ according to Article 3(a) ... and, if so, what are those further or different criteria?

(4) For the purposes of Article 3(a), is a multi-disease vaccine comprising multiple antigens ‘protected by a basic patent’ if one antigen of the vaccine is ‘protected by the basic patent in force’?

(5) For the purposes of Article 3(a), is a multi-disease vaccine comprising multiple antigens ‘protected by a basic patent’ if all antigens directed against one disease are ‘protected by the basic patent in force’?

The CJEU ruled as follows:

(1) Article 3(a) ... must be interpreted as precluding the competent industrial property office of a Member State from granting a supplementary protection certificate relating to active ingredients which are not specified in the wording of the claims of the basic patent relied on in support of the application for such a certificate.

The component active ingredients must be ‘specified’ in the wording of the claims of the basic patent. The answer to the applicant’s dilemma is that the product for which protection is sought in an SPC application must mirror exactly the product identified in the basic patent: an application for an SPC on product A+B+C must be supported by a patent that covers A+B+C (see Table 2), providing, of course, that the MA is for at least the active ingredients in that combination.

### Table 2: The result of the Medeva ruling

<table>
<thead>
<tr>
<th>Patent</th>
<th>MA</th>
<th>SPC</th>
<th>Issue</th>
<th>CJEU Ruling</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A+B+C</td>
<td>A</td>
<td>Is the MA for A+B+C a valid authorisation for an SPC on product A, further to Article 3(b)?</td>
<td>Yes</td>
</tr>
<tr>
<td>A</td>
<td>A+B+C</td>
<td>A+B+C</td>
<td>Is product A+B+C protected by a patent for A alone, further to Article 3(a)?</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 3: Medeva and selected SPC cases decided in the wake of Medeva

<table>
<thead>
<tr>
<th>Case name</th>
<th>Claims of basic patent in force</th>
<th>MA for</th>
<th>SPC/SPC application for</th>
<th>SPC Allowed/disallowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case C-322/10 Medeva BV v Comptroller-General of Patents</td>
<td>Method of making a cellular vaccine against whooping cough combining pertactin and filamentous haemagglutinin (A + B)</td>
<td>Various MAs, all containing pertactin, filamentous haemagglutinin, plus other vaccines. (A + B + various)</td>
<td>Four SPCs, each containing pertactin and filamentous haemagglutinin, plus various other vaccines (A + B + various)</td>
<td>Disallowed further to Article 3(a)</td>
</tr>
<tr>
<td>(First four SPC applications) (A vaccine case)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case C-322/10 Medeva BV v Comptroller-General of Patents</td>
<td>Pertactin and filamentous haemagglutinin (A + B)</td>
<td>Products containing pertactin and filamentous, plus between 8 and 11 further active ingredients e.g. (A + B + C +, etc)</td>
<td>Pertactin and filamentous haemagglutinin (A + B)</td>
<td>Permitted further to Article 3(b)</td>
</tr>
<tr>
<td>(Fifth SPC application)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case C-630/10 University of Queensland v Comptroller-General of Patents</td>
<td>Methods of production of papillomavirus-like particles HPV-6 and HPC-11 (A+B)</td>
<td>Gardasil – containing HPV-6, HPV-11, HPC-16 and HPC-18 (A+B+C+D)</td>
<td>Three SPCs: HPV-6, HPV-11, HPV16 and HPV 18 (ie A+B+C+D) HPV-11 alone (ie B) HPV-6 alone (ie A)</td>
<td>In the case of a basic patent relating to a process by which a product is obtained: Article 3(a) does not allow an SPC for a product that is not identified in the wording of the claims as deriving from the process patented</td>
</tr>
<tr>
<td>(A vaccine case)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case C-6/11 Daiichi Sankyo Company v Comptroller-General of Patents</td>
<td>Biphenylimidazole derivatives, their preparation and their therapeutic use Olmesartan medoxomil is specifically disclosed in the wording of claim 4</td>
<td>Olmotec Plus –olmesartan medoxomil and hydrochlorothiazide</td>
<td>Olmersartan medoxomil and hydrochlorothiazide</td>
<td>Disallowed further to Article 3(a). The combination of active ingredients for which protection is sought is not identified in the wording of the claims of the basic patent</td>
</tr>
</tbody>
</table>
How Must the Product be Disclosed in the Claims of the Basic Patent?

‘Specified’ and ‘Identified’

The CJEU then followed the Medeva ruling in two further decisions delivered very shortly afterwards from parallel references: Daiichi Sankyo Company and University of Queensland. However, in Queensland the language of the CJEU regarding what the basic patent in force must disclose, differed slightly from that in the Medeva ruling. The decisions concerned SPCs on products obtained from a patented process. The CJEU stated:

40 ... just as Article 3(a) of Regulation No 469/2009 precludes the grant of a SPC relating to active ingredients which are not specified in the wording of the claims of the basic patent (Medeva, paragraph 25), where the basic patent relied on in support of a SPC application relates to the process by which a product is obtained, that provision also precludes a SPC being granted for a product other than that identified in the wording of the claims of that patent as the product deriving from that process. The grant of a SPC is not conditional on whether it is possible to obtain a product directly as a result of the process by which the product is obtained, where that process has been the subject of a patent.

41 ... in the case of a basic patent relating to a process by which a product is obtained, Article 3(a) ... precludes a SPC being granted for a product other than that identified in the wording of the claims of that patent as the product deriving from that process. Whether it is possible to obtain the product directly as a result of the process by which the product is obtained, where that process has been the subject of a patent.

As the emphasised words show, between the Medeva and University of Queensland cases there is a distinct difference in language: Medeva refers to the active ingredients being ‘specified’ in the wording of the claims, whereas University of Queensland refers to products being ‘identified’ in the wording of the claims. Although it is generally thought that these terms share the same meaning, it is far from clear what that meaning is, per the Chancellor of the High Court of England and Wales:

The ambit of ‘specified’ may range from express naming, through description, necessary implication to reasonable interpretation. Where on that scale the dividing line is to be drawn will necessitate further references in due course in the light of the facts of the cases in which the issue arises.

Thus having dealt in relatively clear terms with the larger issues of interpreting Article 3(a) and 3(b), the CJEU has introduced a new question for applicants of combination vaccines (and many other products); when has the product for which they seek protection been identified or specified in the basic patent in force – must the active ingredients of a combination vaccine be identified explicitly, or is it sufficient for them to be referred to generically? The distinction is important. Take, for example, a patent claim that is drafted to cover a particular named antigen in combination with an unnamed antigen from a class of antigens to a particular disease agent. If an SPC is later sought for the named antigen in combination with another named antigen that falls within the class claimed, is that second antigen specified or identified by the claims of the basic patent in force?

The National Courts Diverge Again

Pending further referrals to the CJEU (see below) on the meaning of ‘specified’ and ‘identified’, European national courts have again taken divergent views. These fall on a spectrum between what could be described as a liberal approach and a strict approach:

- **Liberal approach**
  - The Court of Appeal in the Hague has held that reference to non-toxic acid addition salts in the basic patent claims supporting an SPC specifically for escitalopram oxalate satisfies the requirement of ‘specified’ in Medeva, even though the oxalate salt itself is never explicitly mentioned. In a different case, the District Court of the Hague has gone further than the Court of Appeal, taking the view in a preliminary decision that whether the product is ‘specified’ is actually a question of whether the combination product is part of the subject-matter of the patent, taking into account...
not only the description and the drawings, but the general knowledge of the man skilled in the art at the priority date.20

- Similarly, in France, the Tribunal de Grande Instance de Paris has stated, when issuing a preliminary injunction, that the word ‘diuretic’ is sufficient to identify or specify the compound HCTZ.

**Strict approach**

- The English Patents Court has held that a patent to a method for producing ‘a molecule with binding specificity for a particular target’ did not contain an adequate level of ‘specification’ to support an SPC on ranibizumab monoclonal antibody, although it commented that the matter was unclear and that a referral to the ECJ would be required.21

**An intermediate approach**

- The Danish Patent and Trademark Office (‘DPTO’) recognises that the combination of the active ingredients must be specified by the wording of the claims of the basic patent in accordance with the Medeva decision of the CJEU. The DPTO says it will consider a product to be specified in the wording of the claims when the product is described by a chemical name. But the guidance also says that the product does not always need to be specifically mentioned, it could instead be covered by a Markush formula. The DPTO then adds that a product may in some cases be considered to be specified in the wording of the claims of the basic patent, if the product is specified by functional terms.

**Back to the CJEU**

This issue has itself now been referred to the CJEU in Actavis Group.22 Whilst this case does not feature vaccines, it does concern an SPC granted to Sanofi for a combination – irbesartan and hydrochlorothiazide. The SPC was granted on the basis of a basic patent for ‘N-substituted heterocycle derivatives, their preparation, compositions containing them’. The question being asked of the CJEU by Arnold J is:

> What are the criteria for deciding whether ‘the product is protected by a basic patent in force’ in Article 3(a) of [the Regulation]?

A further reference has also been made on this question by Warren J in Eli Lilly & Co, specifically drawing out its application to antibody products:23

1. **What are the criteria for deciding whether the product is protected by a basic patent in force in Article 3(a) of Regulation 469/2009/EC?**

2. **Are the criteria different where the product is not a combination product, and if so, what are the criteria?**

3. **In the case of a claim to an antibody or a class of antibodies, is it sufficient that the antibody or antibodies are defined in terms of their binding characteristics to a target protein, or is it necessary to provide a structural definition for the antibody or antibodies, and if so, how much?**

This last question is particularly relevant to the example of a combination of a named antigen with an unnamed antigen from a class, given above. However, the full interpretation of Article 3(a) necessary to guide applicants is still some way away, with rulings by the CJEU not expected on the above questions until the end of 2013 at the earliest.

**Infringement of an SPC by a Combination**

Given the consequences of the Medeva ruling – militating towards an application for an SPC on product A alone, as described above – how is the SPC proprietor’s ability to enforce its SPC for A against third-party use of a combination product containing A (such as A+B+C) affected? This is an important consideration in determining whether, and to what extent, the Medeva decision restricts applicants for combination vaccines in practice.

The answer depends on the interpretation of Articles 4 and 5 of the SPC Regulation:

**Article 4 Subject matter of protection**

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

---

20) Sanofi SA v Pharmachemie BV and Teva Pharma BV and Sanofi SA v Teva Nederland BV, 14 September 2012, Case Nos 425814/KG ZA 12-905 and 426135/KG ZA 12-928. Unlike the Lundbeck decision (above), it is not mentioned in the patent at all in Sanofi.


22) Case C-443/12, referred in Actavis Group PTC EHF & another v Sanofi Pharma Bristol-Myers Squibb SNC [2012] EWHC 2545 (Pat).

Novartis AG v Actavis UK Ltd

This has now been resolved in the affirmative by the CJEU in ingredient.24 However, the Düsseldorf court nonetheless containing valsartan combined with another active ingredient, would be infringed by a medicinal product Vienna held that an SPC granted for a single active ingredient, litigation, the first instance courts of Düsseldorf, Paris and consistent in their approach. In the European valsartan

On this issue, the European national courts have been fairly thought it necessary to refer questions on the matter to the CJEU. The English Patents Court also referred questions to the CJEU on this issue in Novartis AG v Actavis UK Ltd,25 as follows:

*Where a supplementary protection certificate has been granted for a product as defined by Regulation (EC) No 469/2009 for an active ingredient, are the rights conferred by that certificate pursuant to Article 5 of the Regulation in respect of the subject matter as defined in Article 4 of the Regulation infringed:

(i) by a medicinal product that contains that active ingredient (in this case valsartan) in combination with one or more other active ingredients (in this case hydrochlorothiazide); or

(ii) only by a medicinal product that contains that active ingredient (in this case valsartan) as the sole active ingredient?

This has now been resolved in the affirmative by the CJEU in Novartis AG v Actavis UK Ltd:26

Articles 4 and 5 ... concerning the supplementary protection certificate for medicinal products must be interpreted as meaning that, where a ‘product’ consisting of an active ingredient was protected by a basic patent and the holder of that patent was able to rely on the protection conferred by that patent for that ‘product’ in order to oppose the marketing of a medicinal product containing that active ingredient in combination with one or more other active ingredients, a supplementary protection certificate granted for that ‘product’ enables its holder, after the basic patent has expired, to oppose the marketing by a third party of a medicinal product containing that product for a use of the ‘product’, as a medicinal product, which was authorised before that certificate expired.

As a result of the CJEU ruling in Novartis v Actavis, the owner of an SPC for an antigen A, would be able to enforce that SPC against a product comprising A in combination with other antigens or active ingredients. This is important in the context of the Medeva ruling. The Novartis ruling complements Medeva, by confirming a wide scope of enforcement of an SPC for A (against A+B+C etc), which has the effect of counterbalancing the restrictions on the scope of the SPC in Medeva. That is, in circumstances where the patent claims fewer of the active ingredients than are authorised for the therapeutic product (such as A), the SPC applicant should seek to mirror the narrower patent, that SPC will remain enforceable against third-party products that mirror the broader MA. In summary, the CJEU has found a way to make Articles 3(a) and 3(b) work for combination products, albeit subject to clarification of what ‘specified’ and ‘identified’ mean. Unfortunately there is another problem lurking for vaccine SPCs. This is what this article turns to now.

Is an Adjuvant an ‘Active Ingredient’?

Why it Matters

The above discussion reviews the present state of the CJEU SPC cases on combinations of active ingredients. However, the question remains: what exactly is an active ingredient? Is an adjuvant an active ingredient? This is important in the context of vaccines because, as explained above, vaccines are typically not only combinations of antigens, but may also include one or more adjuvants, particularly if they are pure recombinant polypeptides. In turn, this matters commercially because if an adjuvant is an active ingredient, the combination of a new adjuvant with a known antigen (or combination of antigens) may be a product entitled to SPC protection in its own right. If an adjuvant is not considered an active ingredient, no amount of investment in producing new and approved adjuvants for antigens will enable SPC protection.

---

24) The Düsseldorf District Court in Novartis AG v Actavis Deutschland GmbH & Co KG and Actavis Ltd 4b O 66/11, by order of 11 November 2011 (following the holding in preliminary injunction proceedings (case nos 4b O 280/10 and 4b O 287/10) of 8 March 2011); also, see Sanofi-Aventis France and others v Novartis and others, Paris First Instance Court, 31 October 2011 (11/15302), and in the parallel first instance decision of the Vienna Commercial Court, 7 October 2011 (19 Gg 25/11).


26) Case C 442/11, unreported, 9 February 2012.
Why this Question has Gone to the CJEU

It is precisely this situation that gave rise to the statement of Arnold J from GlaxoSmithKline Biologicals SA v Comptroller-General of Patents27 (‘GSK’) that introduced this article. The context in which Arnold J was speaking was an appeal against a decision by the UKIPO28 to refuse two SPC applications by GlaxoSmithKline; one for each of the following:

(1) an adjuvant described as ‘an oil in water emulsion comprising squalene, DL-α-tocopherol and polysorbate 80’ and known as AS03 (protected by EP(UK) 0 868 918);

(2) for ‘an adjuvanted influenza vaccine comprising an influenza virus component which is an influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak or has the potential to be associated with a pandemic outbreak, wherein the adjuvant is [AS03]’ (protected by EP(UK) 1 618 889).

In short, GSK were seeking an SPC on an adjuvant and also on an adjuvant combined with an antigen.

The reason the UKIPO would not allow either application was that AS03 was not considered to be an ‘active ingredient’.

‘Active ingredient’ is found within the definition of ‘product’ in Article 1:

Article 1

... (b) ‘product’ means the active ingredient or combination of active ingredients of a medicinal product ...

In turn, the significance of the definition of ‘product’ is that, further to Article 2, it is the product that is protected by an SPC:

Article 2

Scope

Any product protected by a patent in the territory of a Member State and subject, prior to being placed on the market as a medicinal product, to an administrative authorisation procedure as laid down in 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 or Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products may, under the terms and conditions provided for in this Regulation, be the subject of a certificate.

Consequently, if AS03 is not an active ingredient, it cannot be protected by an SPC in its own right. Nor can it create a product that is a combination of active ingredients, when combined with an antigen active ingredient, for the purpose of Article 1(b).

When addressing whether AS03 is an active ingredient, Arnold J summarised the expert evidence available to him on the role of adjuvants, as follows:

27. The concept that the immune response to antigens can be improved by the addition of certain compounds into the vaccine formulation was demonstrated approximately 100 years ago when aluminium salts were first used in vaccine formulations. Such compounds are referred to as ‘adjuvants’ (derived from the Latin word ‘adjuvare’ which means ‘to help or aid’).

28. The last few decades have seen extensive research and development in the field of adjuvants. There has been a surge in adjuvant technology which has been assisted by a greater understanding of innate and adaptive immunity and their close interaction at the molecular level in the response to a pathogen.

29. It is important to be clear as to exactly what an adjuvant does and what it does not do. It is something which aids the process of generating an antigen-specific antibody response, but it does not generate antibodies itself. The main way in which an adjuvant works is to amplify the immune response.

30. What an adjuvant does is to provide a quantitative change in the immune response which in turn leads to a qualitative change in the immune response. The first thing the adjuvant can do is to stimulate cytokine production, a general immune response that is not specific to any antigen. The second thing the adjuvant can do is to stimulate the antigen presentation of APCs. This leads to stimulation of the adaptive
immune response, which leads to a greater generation of antigen-specific antibodies.

31. These quantitative effects are of value in themselves since they enable antigen-sparing. In addition, however, they lead to a qualitative effect which is greater cross-reactivity. When the body is exposed to an antigen, it normally produces what is described as a polyclonal response. That is to say, it does not just generate one antibody to the antigen, rather it generates a group of different antibodies which will be specific to different parts (epitopes) of the antigen. Within that polyclonal group, a small proportion will bind not only to that antigen, but also to related antigens. That is referred to as cross-reactivity. Because adjuvants cause more antibodies to be produced, this can result in increased cross-reactivity.

The judge then had to decide whether, according to these terms, an adjuvant could be regarded as an ‘active ingredient’. In order to guide himself on this question, the judge drew on a number of earlier rulings of the CJEU in similar cases. In particular, in Case C-431/04 Massachusetts Institute of Technology29 (‘MIT’) (see Table 4), an SPC was not permitted on a combination of the cytotoxic agent carmustine and the polymeric matrix polifeprosan. This is because polifeprosan was not regarded on the evidence as an active ingredient, and therefore the CJEU ruled that it could not form a combination product with carmustine capable of SPC protection.30 Arnold J summarised the CJEU’s reasoning in MIT like this:

(i) the expression ‘active ingredient’ was generally accepted not to include substances forming part of a medicinal product which did not have an effect (which in context must mean a therapeutic effect) of their own on the human or animal body;

(ii) this understanding was consistent with paragraph 11 of the Explanatory Memorandum in the Commission’s original Proposal for the Regulation [‘(Explanatory Memorandum’)], indeed it was apparent from the Memorandum that ‘product’ was understood to mean an ‘active ingredient’ in the strict sense;

(iii) accordingly, a substance which did not have any therapeutic effect of its own and which was used to obtain a certain pharmaceutical form of the medicinal product was not an ‘active ingredient’;

(iv) therefore an alliance of such a substance with one that did have a therapeutic effect of its own was not a ‘combination of active ingredients’;

(v) it was immaterial that the substance without any therapeutic effect of its own rendered possible a pharmaceutical form of the medicinal product necessary for the therapeutic efficacy of the substance which did have a therapeutic effect;

(vi) indeed, a test which involved considering whether a substance without any therapeutic effect of its own rendered possible a pharmaceutical form of the medicinal product necessary for the therapeutic efficacy of another substance which did have a therapeutic effect would create legal uncertainty and inhibit the attainment of a uniform solution at Community level.

It is on the basis of these principles in MIT that the UKIPO refused the GSK application, drawing a parallel between AS03 and polifeprosan to conclude that neither are active ingredients within the meaning of Article 1(b) SPC Regulation – AS03 had no therapeutic effect and did not itself confer any immunity. In GSK, Arnold J also reviewed two cases in which the CJEU had made a strict interpretation of ‘product’ in Article 1(b), albeit that these were in the context of SPC applications for subsequent therapeutic uses of an active ingredient. In these cases, the CJEU had ruled that the definition of product is not concerned with the therapeutic use of the active ingredient (see Case C-31/03 Pharmacia and Case C-202/05 Yissum in Table 3).

This strict interpretation of ‘product’ in these two contexts and comparison with MIT would, on the face of it, seem to be a straightforward one in GSK and it seems the judge might have come to the conclusion that an antigen is not an active ingredient and that there is no need to refer questions to the CJEU. That is, were it not for another recent CJEU ruling in Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents.31 Neurim has now brought into question the strict interpretation of Article 1(b) and caused the lack of clarity that Arnold J laments in GSK.

30) Had there not been an earlier MA for carmustine than the one cited in the application then it might have been possible to obtain the SPC on carmustine alone.
31) Case C-130/11, unreported, 19 July 2012.
### Table 4: Decisions exemplifying the ‘strict’ approach, and the Neurim ‘teleological approach’

<table>
<thead>
<tr>
<th>Case</th>
<th>Basic patent in force</th>
<th>Earlier MA</th>
<th>MA relied upon for SPC</th>
<th>SPC/SPC application for:</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case C-431/04 Massachusetts Institute of Technology</strong>32</td>
<td>Patent protecting carmustine and polifeprosan</td>
<td>Carmustine with inert excipients</td>
<td><em>Gliadel</em> – carmustine active ingredient and polifeprosan as excipient</td>
<td>Combination: 1. Carmustine (a cytotoxin) 2. polifeprosan (a polymeric biodegradable matrix)</td>
<td>SPC refused on combination because it is not a combination of active ingredients within the meaning of Article 1(b). That is, polifeprosan is not an active ingredient and so the ‘product’ is carmustine, which is the subject of an earlier MA</td>
</tr>
<tr>
<td><strong>Case C-31/03 Pharmacia Italia SpA</strong>33</td>
<td>Patent protecting cabergoline</td>
<td><em>Galastop</em> – cabergoline (active ingredient) for veterinary use</td>
<td><em>Dostinex</em> – cabergoline (active ingredient) for human use</td>
<td>Cabergoline</td>
<td>An SPC was not permitted, because cabergoline had already been authorised for veterinary use34</td>
</tr>
<tr>
<td><strong>Case C-202/05 Yissum Research and Development Company of the Hebrew University of Jerusalem v Comptroller-General of Patents</strong>35</td>
<td>Second medical use patent claiming calcitriol in topical treatment of skin disorders including psoriasis</td>
<td>Two; both containing calcitriol as the active ingredient: <em>Calcijex</em> and <em>Rocaltrol</em>, authorised for the management of hypocalcaemia in patients undergoing dialysis for chronic renal failure; and, for chronic renal failure or post-menopausal osteoporosis, respectively</td>
<td><em>Silkis ointment</em> – calcitriol (active ingredient) with various carriers for the treatment of psoriasis</td>
<td>Calcitriol alone or in combination with an ointment base</td>
<td>SPC refused: ‘Product’ in Article 1(b), must be interpreted strictly to mean ‘active ingredient’. Hence, the concept of ‘product’ cannot include the therapeutic use of an active ingredient protected by the basic patent</td>
</tr>
</tbody>
</table>

### The ‘teleological’ approach to the meaning of ‘product’ and interpretation of Article 1(b)

| Case | Two patents: Protecting melatonin as used in *Regulin*; and, Protecting melatonin as used in *Circadin* | *Regulin* – melatonin for regulating the seasonal breeding activity of sheep | *Circadin* – melatonin for the treatment of insomnia in humans | Use of melatonin in the treatment of human insomnia | The SPC on melatonin for use in the treatment of human insomnia is permitted, even though the melatonin active ingredient has been the subject of a previous MA (for use in sheep) |

---

33) [2004] ECR I-10001.  
34) The case is actually concerned with Article 19(i) and not Article 1(b). However, it is stated in Pharmacia that the decisive factor for the grant of a certificate is not the intended use of the medicinal product, and also that the purpose of the protection conferred by the certificate relates to any use of the product as a medicinal product, without any distinction between use of the product as a medicinal product for human use as a veterinary product.  
36) [2012] ECR I-0000.
The Problem Caused by Neurim

In Neurim, the CJEU ruled that an SPC could be granted to protect melatonin for the treatment of insomnia in humans on the basis of the MA granted in 2007 for this use. This is despite the fact that this active ingredient had been used, further to a MA of 2001, for regulating the seasonal breeding activity of sheep. At first instance, it was again Arnold J who had held that the authorities in favour of a strict approach, discussed above (and see Table 3), meant that he had to find that no SPC could be granted on the basis of a MA for a different therapeutic use, when melatonin had already been the subject of a marketing authorisation. However, on appeal, it was in referring the matter to the CJEU that Jacob LJ made his criticism that the strict interpretation of the SPC Regulation had created a system that was ‘not fit for purpose’ (see above).

There are several points subsequently made by the CJEU in its eventual Neurim judgment that make interesting reading in the light of Jacob LJ’s criticism:

The reason given for the adoption of the SPC Regulation is the fact that the period of effective protection under the patent is insufficient to cover the investment put into pharmaceutical research and the regulation thus sought to make up for that insufficiency by creating an SPC for medicinal products...

It is apparent from [the Explanatory Memorandum], that, like a patent protecting a ‘product’ or a patent protecting a process by which a ‘product’ is obtained, a patent protecting a new application of a new or known product, such as that at issue in the main proceedings, may, in accordance with Article 2 of the SPC Regulation, enable an SPC to be granted...

Therefore, if a patent protects a therapeutic application of a known active ingredient which has already been marketed as a medicinal product, for veterinary or human use, for other therapeutic indications, whether or not protected by an earlier patent, the placement on the market of a new medicinal product commercially exploiting the new therapeutic application of the same active ingredient, as protected by the new patent, may enable its proprietor to obtain an SPC, the scope of which, in any event, could cover, not the active ingredient, but only the new use of that product.

Without any reference to the cases ruling that a strict interpretation of ‘product’ is necessary, the CJEU in Neurim held that SPC protection for a second and subsequent use of a known active ingredient was permissible. It does not matter that there is a MA for active ingredient alone that is earlier than the one being relied upon.

It is with Jacob LJ’s comments still fresh, about the damage done to the investment in research if the SPC system fails to protect second medical use patents, that the CJEU has taken such an apparently new course in Neurim. Indeed, the reference to the purpose of the SPC Regulation to protect investment and ‘new medicinal products commercially exploiting the new therapeutic application’ suggests that the CJEU has the Court of Appeal judgment very much in mind.

Although Neurim concerns an SPC application for a second therapeutic purpose for melatonin and not whether an adjuvant is an active ingredient, it has an impact on the latter issue. This is because it takes what is referred to in the decision as a ‘teleological’ construction of ‘product’ rather than a strict one. In other words, when deciding what a product is, it looks to the purpose of the SPC Regulation. That is, very broadly, to provide sufficient cover to protect the investment made in products. Indeed, this is exactly the rationale being tested by the applicant in GSK when seeking SPC protection for a combination of AS03 and antigen. In particular, Counsel for GSK also relied upon the Explanatory Memorandum to the SPC Regulation as saying that the SPC Regulation was intended to apply to all new products which were the subject of innovative research. Furthermore, the applicant cites the words of the CJEU in an earlier case, stating that the fundamental objective of the SPC Regulation is to ‘ensure sufficient protection to encourage pharmaceutical research, which plays a decisive role in the continuing improvement in public health’.38

There is another strand to the applicant’s case in GSK, which is to seek to distinguish the MIT case by saying that only minor variants such as new doses, different salts and esters, and different formulations, are intended to be excluded as...
active ingredients for the purpose of defining the products. Polifeprosan in MIT is an example of such a minor variant, because in and of itself it has no physiological effect on the body. By contrast, it is argued, AS03 does have such a physiological effect on the body, allowing for the effect of the antigen to be enhanced. This is sufficient, it is said, for it to be considered an active ingredient forming the basis of a product and therefore capable of SPC protection.

Because of the apparent conflict between strict and teleological approaches now presented, Arnold J was compelled to refer to the CJEU the following questions in GSK:

1) Is an adjuvant which has no therapeutic effect on its own, but which enhances the therapeutic effect of an antigen when combined with that antigen in a vaccine, an 'active ingredient' within the meaning of Article 1(b) of Regulation 469/2009/EC?

2) If the answer to question (1) is no, can the combination of such an adjuvant with an antigen nevertheless be regarded as a 'combination of active ingredients' within the meaning of Article 1(b) of Regulation 469/2009/EC?

The CJEU Reaches a Fork in the Road

A positive answer to either of these questions about antigens from the CJEU would signal that it intends to continue the more commercial, teleological approach to SPCs, and this will open up many new opportunities to extend protection for vaccines. It would also corroborate the Neurim decision in respect of further therapeutic use. It would further suggest that other patented products based on an earlier active ingredient that have hitherto not been eligible for patent protection may now potentially be the subject of SPCs.

A negative answer to both questions would, however, leave the Neurim decision even more isolated than it already appears to be on the basis of the earlier, strict authorities.

The path being taken in decisions by the CJEU on the SPC Regulation has, therefore, come to a crossroads. Just as the flurry of cases that began with Medeva appeared to clarify the circumstances in which SPC protection could be obtained for a combination product (as discussed in the first half of this article), the apparently radical decision in Neurim has emerged to potentially turn our understanding of the SPC system upside down.

It is an irony that it was the attempt of the CJEU to deal with the commercial inadequacies of the SPC Regulation pointed to by Jacob LJ in the English Court of Appeal that has led to the CJEU Neurim ruling and Arnold J's exasperated criticism in GSK (both quoted at the beginning of this article). The effect of Arnold J's remarks is that the CJEU needs to make up its mind about whether the SPC Regulation protects the wider class of pharmaceutical inventions beyond new active compounds alone, and stick to it, in clear decisions. GSK is the decision in which to do that, and vaccine protection is the issue that is right at the heart of it.