Extended protection for pharmaceutical patents in Europe: where are we now?

The end of 2013 was a busy time at the Court of Justice of the European Union (CJ), with rulings in a number of references from national courts concerning supplementary protection certificates (SPCs) which extend the term of protection for pharmaceutical patents. This is a seemingly simple concept yet has led to a thicket of litigation. Earlier in 2013, a leading patents judge described the SPC system as “dysfunctional”.

In this Advisory we discuss whether the CJ’s recent rulings clarify things (or have the opposite effect), and give practical guidance on what the decisions mean for innovators and where uncertainties remain.

Summary
The recent CJ rulings give rise to as many questions as they answer, and we can expect many more national court references to the CJ. The key points arising from the CJ’s rulings may be summarised as follows:

- Combining a patented active ingredient with any ingredient having no independent therapeutic effect will not provide new basis for SPC protection over the original active ingredient.
- Combining a patented active ingredient with a second active ingredient will not provide new basis for SPC protection extending beyond that available for the original active ingredient unless (a) the original basic patent also protects the second active ingredient and the combination of the two, or (b) the combination is protected by a separate (or possibly the same) basic patent and is patentable over and above the patentability of the original active ingredient.
- Broad early-stage patents are unlikely to provide basis for an SPC application unless they specifically identify the active ingredient, whether explicitly or implicitly.
- Second medical use patents may form the basis for an SPC, in certain circumstances.
- Approvals in Switzerland which are automatically recognised in an EEA state (Liechtenstein) can qualify as the “first authorisation” which determine the duration of an SPC, but cannot be the basis for an SPC application.
To try to avoid the uncertainty, innovators should look to observe the following points to maximise the chances of getting SPC protection:

1. Be as specific as possible when drafting patent claims. There is little harm in having some very specific dependent claims to make sure possible medicinal products are “protected”.
2. Look to amend granted patents which have claims to general classes of active ingredients, where there is basis in the patent specification to do so.
3. File follow-on patents once particularly useful sub-classes or individual active ingredients have been identified.
4. When prosecuting patent applications, look to separate out applications which relate to combination products.
5. File second medical use patents and seek SPC protection based upon those.
6. Beware of seeking regulatory approvals in ex-EU countries, such as Switzerland, which have customs unions with EEA member states, without understanding the possible consequences for SPC duration.

**SPCs for medicinal products**

It takes many years to secure a marketing authorisation (MA) to place a new medicinal product on the market due to the importance of ensuring the safety and efficacy of such products. Often the 20-year period of protection under a patent is insufficient to recover the investment put into research and development. In order to improve the protection of innovation in the pharmaceutical sector, the SPC Regulation provides for an additional period of protection if the first MA in the EEA is not granted until more than 4.5 years after the patent is filed, by the grant of an SPC which commences on the expiry of the patent.

The duration of an SPC is equal to the period elapsed between patent filing and grant of the first MA in the EEA, less five years, and subject to a maximum duration of five years, that is, expiring 15 years after the expiry of the patent, whichever is the earlier. The Paediatric Regulation provides for a six-month extension to the SPC term for certain products on which trials are completed in accordance with an approved Paediatric Investigation Plan. This applies regardless of whether the results are positive or negative.

SPCs and paediatric extensions are granted by the patent offices in each EU member state and are broadly similar to the patent term extensions available under the Hatch-Waxman Act in the US. However, the scope of an SPC is narrowed to the particular medicinal product that has been authorised, as opposed to a simple extension of the patent term.

The conditions for obtaining an SPC in each EU member state are as follows:

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 EU rules.
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.

A potential 5.5 year extension of protection for a successful product in key markets can be worth many billions of dollars to a pharmaceutical innovator. Driven by this fact, there has been much litigation which has led to an inconsistent interpretation of the SPC Regulation by both national patent offices and the CJ. The recent slew of references to the CJ aimed to achieve some much-needed clarity.

The current state of the SPC system can be explored by reference to the following four questions:

1. What is the “product”?
2. What is meant by “protected by a basic patent”?
3. What happens when a single basic patent protects more than one “product”, or where one “product” is covered by multiple basic patents?
4. What can be a “valid authorisation” and therefore what is the “first authorisation”?

**Q1. What is the “product”?**

The SPC Regulation defines “product” as the active ingredient or combination of active ingredients of a medicinal product.
Patent offices in different member states have been adopting different approaches to SPCs for adjuvants – agents which are included in vaccines to enhance the patient’s immune response to the administered antigen but have no independent therapeutic effect. In Glaxosmithkline Biologicals® the English Patents Court asked the CJ whether such an adjuvant can be treated as an “active ingredient” or, when combined with an antigen, as part of a “combination of active ingredients” for SPC purposes. The CJ held that any ingredient having no independent therapeutic effect was not an “active ingredient”, nor could it be part of a “combination of active ingredients”.

It appears, therefore, that any kind of reformulation to improve a medicinal product, including (in the context of vaccines) the addition of an adjuvant, will not give basis for an SPC. Combining the original active ingredient with other active ingredients might give basis for an SPC, provided the other requirements are met (see Q3 below). However, similar issues are now before the CJ in two pending references.

Q2. What is meant by “protected by a basic patent”? In 2011, in the Medeva case, the CJ said that to be “protected” by the basic patent the active ingredient(s) of a product must be “specified in the wording of the claims of the basic patent”. In reaching this conclusion, the CJ rejected what had become known as the “infringement” test, i.e., that a product was “protected” if it would infringe the claims of a patent. In doing so, the CJ made it clear that something more was required, but the national courts have continued to struggle to identify what is that something extra.

In Eli Lilly® the CJ sought to tackle this problem. The holder of the basic patent was Human Genome Sciences (HGS), although the active ingredient in question, tabalumab, was developed following additional research by a third party, Eli Lilly. Tabalumab was not expressly identified in the claims of the basic patent (or indeed the specification), although if defined functionally it was clear that it would infringe the claims of HGS’s basic patent which covered “[a]n isolated antibody or portion thereof that binds specifically to [Neutrokine-α or the extracellular domain thereof].”

The CJ ruled that a structural definition of the active ingredient(s) in a product was not required: a functional definition would suffice, provided that the claims “relate, implicitly but necessarily and specifically, to the active ingredient in question”. While leaving the ultimate decision to the national courts, the CJ indicated that an SPC may not be available in circumstances “where the patent holder has failed to take steps to carry out more in-depth research and identify his invention specifically”. In other words, and starting from the teaching in the basic patent, if further work is required to get to the active ingredient, the product may not be “protected” by the basic patent (even if the active ingredient would infringe the basic patent).

Although the CJ’s comments in Eli Lilly are of a general nature and the specific facts of each case will be very material, the message here is that broad, early-stage patents may not provide basis for SPCs that concern products that include active ingredients determined only after significant additional research. This underlines the importance of filing applications for additional patents once specific active ingredients have been identified.

Q3. What happens when a single basic patent protects more than one “product”, or where one “product” is covered by multiple basic patents? It has long been the practice of patent offices across Europe to allow a single basic patent to form the basis of SPC applications in relation to different products. Although untested in CJ jurisprudence, that logically followed from the CJ’s comments in Biogen® where the court held that SPCs could be granted for different basic patents which all protected the same product. This approach was termed “one SPC per product, per patent”.

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7. Forsgren, Case C-631/13 and Bayer Cropscience, Case C-11/13.
8. Per the CJ’s reasoned order in Novartis v Actavis, Case C-442/11.
9. Medeva, Case C-322/10, a reference from the English Court of Appeal.
10. Eli Lilly, Case C-493/12, again a reference from the English Patents Court.
11. HGS had developed its own Neutokine- antibody, BENLYSTA (belimumab) which was also within the scope of the same claim of the basic patent. However, belimumab was also the subject of a separate patent and HGS had been granted a UK SPC for belimumab on the basis of the later patent.
12. Biogen, Case C-181/95.
13. AHP Manufacturing, Case C-482/07.
In Medeva, the CJ relied on Biogen for the proposition that “where a patent protects a product ... only one certificate may be granted for that basic patent”. That passage said nothing about the situation where a patent protects more than one product, but the Dutch court was concerned that this may have changed the “one SPC per product, per patent” approach.

In Georgetown University14 (the Dutch referral) and Actavis v Sanofi15 (an English referral with similar facts) the CJ said that, in principle, more than one SPC can be granted in relation to a single basic patent provided that each SPC related to a different product, each of which was protected by the basic patent.

In Georgetown the basic patent protected a number of different human papillomavirus genotypes for use in vaccines, both individually and in combinations. Two MAs were obtained: one relating to a combination of four genotypes (HPV-6, -11, -16 and -18; Gardasil), and subsequently another relating to just two of those genotypes (HPV-16 and -18; Cervarix). The patent holder, Georgetown, was granted SPCs covering each of those combinations based on the same basic patent but the two different MAs. Georgetown also sought an SPC for HPV-16 alone, relying upon the Gardasil MA. The Dutch patent office argued that a second SPC based on the same basic patent and the same MA could not be granted. The CJ held that the SPC for HPV-16 alone was not precluded, as the combination products were different “products” to HPV-16, and each of those “products” was separately protected by the basic patent.

In Actavis v Sanofi the “core inventive advance” of the basic patent related to a family of compounds which included, in particular, irbesartan. Irbesartan was approved and marketed as Aprovel, and an SPC was granted on the basis of the basic patent and the Aprovel MA. The basic patent also claimed irbesartan in combination with “a diuretic”. No specific diuretic was identified in the claim or in the patent specification. The combination of irbesartan and hydrochlorothiazide (HCTZ, a known diuretic) was subsequently approved and marketed as CoAprovel. The patentee, Sanofi, sought a second SPC based on the basic patent and the CoAprovel MA.

The CJ did not address the question of whether the product irbesartan + HCTZ was “protected” by the basic patent, and instead based its reasoning on Article 3(c) SPC Regulation (i.e., whether the product had already been the subject of an SPC). It held that the grant of a second SPC was precluded by Article 3(c) because HCTZ was not separately protected by the basic patent. Thus an SPC for irbesartan + HCTZ would “in fact be connected, wholly or in part” with the same product as the earlier SPC for irbesartan alone. Moreover, for the duration of the first SPC, Sanofi could prevent third parties from marketing any product comprising irbesartan (including irbesartan + HCTZ). A second SPC covering the combination would provide an unwarranted extension.

These decisions are unsatisfactory as they appear to rewrite Articles 3(a) and (c) into a new composite test for combination products, whereby it is required that both the combination of active ingredients and each individual active ingredient must be protected by the basic patent. There is no apparent basis for the second part of that test in the SPC Regulation and it must be doubted whether it will be followed in future cases, leading to yet more uncertainty in this area.

It is clear from the judgment in Actavis v Sanofi that the CJ was critical of reliance on claims to active ingredients “not protected as such by the basic patent but simply referred to in general terms, such as ... ‘beta-blocking compound’, ‘calcium antagonist’, ‘diuretic’, ‘non-steroidal anti-inflammatory’ or ‘tranquilizer’”. The difficulty caused by Actavis v Sanofi is the erroneous attempt to address that via Article 3(c) rather than by holding that the product was not protected by the basic patent contrary to Article 3(a).

More helpfully, Actavis v Sanofi also noted that “if a combination consisting of an innovative active ingredient in respect of which an SPC has already been granted and another active ingredient, contrary to Article 3(a).

14 Georgetown University, Case C-484/12.
15 Actavis v Sanofi, Case C-443/12.
16 Actavis v Sanofi, paragraph 41.
which is not protected as such by the patent in question, is the subject of a new basic patent…, the new patent could, in so far as it covered a totally separate innovation, confer entitlement to an SPC for that new combination”. It would appear that there is no reason to require a new basic patent, so long as in the first patent the combination is “protected” and the claim to the combination is itself novel and inventive.

Some of these issues may fall away when the CJ addresses the issues in Actavis v Boehringer Ingelheim, which relates to Boehringer Ingelheim’s product MicardisPlus (telmisartan + HCTZ)\(^\text{17}\). In this case, the basic patent includes a claim which specifically identifies the combination of telmisartan with HCTZ, rather than a generic reference to a “diuretic”; this would seem to meet the Eli Lilly test for protection of the combination.

While we wait for the CJ’s decision in the Actavis v Boehringer Ingelheim reference, the message appears to be that when considering the potential for SPC protection for follow-on combination products, patents should ideally include claims which clearly specify intended combinations, rather than refer to classes of active ingredients. It may be possible to achieve a similar result by way of amendment should there be basis in the patent specification to do so, or by the filing of divisional applications\(^\text{18}\).

Q4. What can be a “valid authorisation” and therefore what is the “first authorisation”? It is established in CJ jurisprudence that where a product was first placed on the market in the EU as a medicinal product for human use pursuant to an MA granted otherwise than in accordance with the Community Code\(^\text{19}\), that has the effect of rendering the product ineligible for the grant of an SPC\(^\text{20}\).

There is a separate line of cases concerning the situation where the first authorisation was in a non-EU member state, but was automatically recognised in an EEA state. Under the Swiss-Liechtenstein customs union, MAs granted in Switzerland, a non-EEA state, are automatically recognised in Liechtenstein, which is a member of the EEA\(^\text{21}\).

In Novartis\(^\text{22}\) two medicinal products had been authorised in Switzerland several months before obtaining EU authorisations. The CJ held that the Swiss MA was the first MA for the purposes of calculating the SPC duration, by consequence of its automatic recognition in Liechtenstein. Notwithstanding this decision, patent offices in a number of EU member states continued to ignore Swiss MAs when determining SPC durations. This led to the English Patents Court reference in AstraZeneca\(^\text{23}\). In that case, the medicinal product Iressa (gefitinib) had been authorised in Switzerland under a fast-track procedure in March 2004, but the authorisation was later suspended; an EU MA was subsequently granted in June 2009, and the Swiss suspension lifted on 8 December 2010.

The CJ ruled that Iressa was eligible for an SPC, but its duration had to be calculated by reference to the Swiss MA as the “first MA”. The message here is to ensure that ex-EU MA filings will not take effect anywhere in the EEA, if the timings are such that they could prejudice the duration of an SPC based on a later EU MA.

Finally, the CJ’s decision in Neurim\(^\text{24}\) means that there is uncertainty around the meaning of “first authorisation”. Neurim developed a prolonged-release formulation containing the active ingredient melatonin for use as an insomnia medicine (Circadin) and patented this formulation. Following a full application requiring clinical trials, it took 15 years for Circadin to be granted an MA. However, Neurim’s subsequent UK

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17 Actavis v Boehringer Ingelheim, Case C-577/13, a case referred by the English Patents Court prior to the CJ’s decisions in Actavis v Sanofi and Georgetown.
18 From 1 April 2014 divisional applications may be filed at any time, provided the parent application is still pending. This rule change repealed the rule, introduced in 2010, which required any divisional applications to be made within 24 months of the first examination report in a family of applications.
20 Synthon, Case C-195/09; Generics, Case C-427/09.
21 Swiss MAs have different requirements to Directive 2001/83/EC authorisations but, by virtue of Council Decision 1/95, any MA granted in Liechtenstein (including automatically recognised Swiss MAs) is to be treated as an MA granted in accordance with Directive 2001/83. Since 1 June 2005, the automatic recognition of Swiss MAs in Liechtenstein is delayed by a period of 12 months.
22 Novartis and Others, Joined Cases C-207/03 and C-252/03.
23 AstraZeneca AB, Case C-617/12.
24 Neurim, Case C-130/11.
SPC application was rejected on the basis that the “product” was the same as an earlier medicinal product that had been granted an MA, an implant for improving the reproductive performance of sheep (Regulin) in which the active ingredient was also melatonin.

The CJ ruled that the UK Patent Office had been wrong to reject the SPC application – Neurim should not be precluded from obtaining an SPC because the earliest authorisation (i.e., for Regulin) was not within the scope of the basic patent and was therefore not the “first authorisation” for SPC purposes. The message here is that the door may be open for SPC applications based on second medical uses of known medicinal products. However, the unusual, and perhaps extreme, facts in Neurim may result in that case having only narrow precedential application.

**Postscript**

It should not be forgotten that the Regulation does appear to be working as intended in the vast majority of cases, despite the weaknesses in specific areas, such as for combination products. For instance, in the United Kingdom, 203 SPCs were granted and only 15 were rejected by the Intellectual Property Office between 2008 and 2013. The position was similar after grant: in the same period, 222 SPCs expired naturally and only 12 were invalidated (often due to lapse or revocation of the underlying patent rather than problems with the SPC itself). Given the relatively low cost of filing an SPC application, and the potentially valuable protection provided, those rates are quite remarkable.

There are rumours growing that the EU legislature is considering amending the SPC Regulation in response to the extensive criticism. Improvements can be best achieved by ensuring the involvement of patent as well as regulatory specialists in framing the amendments. At the same time it is important that any amendments to the SPC Regulation do not unnecessarily damage the existing system by introducing fresh uncertainties in areas where it is currently operating effectively. In the meantime, innovators are left to negotiate the current system in the best way they can.