European patent term extensions for combination pharmaceutical products

Patent term extensions in Europe take the form of Supplementary Protection Certificates (SPCs), which exist to compensate patentees in Europe for the long time it can take to get pharmaceutical products to market. SPCs are available for medicinal products and can be extended when the product has been tested for paediatric use.

This system allows a patentee for a pharmaceutical product to obtain an extension of protection, beyond the patent term, for up to 5.5 years.

There is no SPC covering the whole of Europe. It is necessary to apply for an SPC in each country of interest.

SPC protection for combination pharmaceutical products, where the medicinal product contains a combination of active ingredients, is currently one of the most contentious areas in the granting of SPCs. A number of referrals to the Court of Justice of the European Union (CJEU), the highest court in Europe, have occurred over recent years to test what is required to obtain SPC protection, particularly where the patentee has already obtained an SPC for a medicinal product containing one of the active ingredients.

Overview

In order to obtain an SPC for a combination of active ingredients of a medicinal product:

- The combination of active ingredients (e.g. A + B) must be protected by the basic patent; and
- The combination of active ingredients must be subject to a valid authorisation (MA) to place the combination of active ingredients on the market in the European country where the SPC is applied for.

The Decisions

In 2011, the CJEU explained how to obtain Supplementary Protection Certificates (SPCs) for combination products in decisions in two similar cases, Medeva and Georgetown et al.

Those decisions had far-reaching consequences for the pharmaceutical and plant protection industries.

In the two cases, the marketing authorisation related to a product which did not have the same active ingredients as those protected by the patent. The CJEU decided that, in cases of such a mismatch, an SPC can still be directed to the patented active ingredients.

If the patent protects only A, an SPC can be directed to A, even if the marketing authorisation is for A + B. Where a marketing authorisation is for A + B + C, but the patent only protects A + B, the SPC can be for A + B, and so on.

The table below provides a summary of the situations in which an SPC is possible:

Patent	SPC	MA	Allowed?
A	A	A	YES
A	A+B	A+B	NO
A	A	A+B	YES
A	A	A+B+C+...	YES
A+B	A+B	A+B	YES
A+B	A+B	A+B+C+...	YES

A+B	A+B	A	NO
A+B	A	A	NO

This is good news for the vaccine industry. Many vaccines combine a number of active ingredients in an authorised product, but not all of those active ingredients are protected by a single patent. Following the CJEU decision, the manufacturer may be entitled to an SPC for the patented active ingredients (if the marketing authorisation is the first for those ingredients).

These decisions were good news for applicants who want SPCs for combination products, where there is a mismatch between the marketing authorisation and the patent claims.

However, a number of issues remained unresolved with respect to SPCs for combination products.

Some of those issues were answered by the CJEU in a raft of decisions handed down in December 2013:

Actavis Group v Sanofi(C-443/12)

Eli Lilly v HGS(C-493/12)

Georgetown University(C-484/12)

Glaxosmithkline Biologicals SA(C-210/13)

A further decision in March 2015 also answers additional questions:

Actavis v Boehringer(C-577/13)

We explain these issues below:

How to determine infringement of an SPC?

The CJEU reviewed infringement of SPCs and decided that an SPC for a single active ingredient can be infringed by a combination drug containing the ingredient.

How to determine what is the "product" of the marketing authorisation?

The CJEU decided that an SPC can be directed to the patented product when the product of the marketing authorisation contains not only the claimed active ingredients, but also other active ingredients.

If the marketing authorisation relates to a combination of more active ingredients (A + B + C) than claimed in the patent (A + B), an SPC can cover the claimed product, i.e. A + B.

The CJEU qualified this with the crucial point that such a marketing authorisation must represent the first authorisation of any product containing the claimed combination of active ingredients. So the marketing authorisation must be the first to cover A + B alone or with other active ingredients.

How to determine what is "protected by" the patent?

The CJEU decided that the product, "protected by" the patent, is specified in the claim wording, but did not explain how much detail was needed for the product to be "specified".

Previously, the UK Intellectual Property Office (UK-IPO) has granted an SPC for the product A + B where the patent claimed A, together with a carrier and, optionally, other therapeutic ingredients. The UK-IPO deemed that the claims covered A + B even though B was not explicitly recited.

It is questionable whether the UK-IPO would now grant such an SPC, in particular whether it would deem B to be "specified" in that claim. Whether a claim to A in combination with an antibody (where B is a known antibody) would be considered to protect A + B is similarly uncertain.

The CJEU did give some guidance, however. It stated that, if a patent claims a product having two active ingredients, but does not claim an active ingredient individually, an SPC cannot cover that ingredient alone.

Since then, a number of national Courts have tried to apply this test and found that serious questions still arose as to the boundaries of the test. Therefore, questions were again referred to the CJEU.

One question, which was referred in the Lillycase, was whether an active ingredient needs to be identified in the claims by a structural formula or whether a functional formula suffice.

In particular, the CJEU was asked whether an SPC is possible where the product is an antibody which is defined in the claims of the basic patent in functional terms (antibody binding to a particular target antigen).

The CJEU decided that for a product to be protected by a basic patent in force, it is not necessary for the active ingredient to be identified in the claims by a structural formula.

Where the active ingredient is covered by a functional formula in the patent claims, it may be possible to obtain an SPC, provided that the claims, when interpreted in the light of the description relate "implicitly but necessarily and specifically" to the active ingredient.

The CJEU has left the interpretation of the claims to the national Courts. Therefore, we will have to wait and see how the national Courts decide whether the claims relate "implicitly but necessarily and specifically" to the active ingredient. For many cases, it is difficult to see how this should be interpreted at a general level and is thus likely to come down to a case-by-case basis.

How many SPCs per patent?

Before the CJEU delivers its decision, the Advocate General (AG) is asked to deliver a non-binding opinion.

The AG argued that only one SPC could be granted for any one patent. This opinion was based on a previous CJEU decision. This was a shock to those in the field, who had interpreted the decision to restrict SPCs to only one SPC per product, per patent. For many years national authorities have allowed multiple SPCs for single patents, based on this interpretation.

The CJEU chose not to confirm whether or not this approach was correct or whether national authorities should only allowed one SPC per patent regardless of how many products are protected by the patent, preferring merely to restate its earlier decision on the point. In the decisions handed down in December 2013, the CEJU was asked to comment further on how many SPCs you can have per patent, which they did, but the answer was not straightforward.

The CJEU ruled that in most circumstances multiple SPCs for different products may be obtained under a single patent.

In the *Georgetown* case, the CJEU was asked whether multiple SPCs can be granted based on a single patent for different products, and whether an applicant can surrender an earlier granted SPC if they are only allowed one SPC per patent. Similar questions were asked in the *Actavis Group v Sanofi* case.

Georgetown's SPC applications related to cervical cancer vaccines (Gardasil® and Cervarix®) comprising multiple antigens, where each antigen was described for the first time in the basic patent. Georgetown had applied for multiple SPCs on the basis of this single patent for the antigens alone and various combinations of the antigen, based on the same marketing authorisation. Therefore, all the SPCs would expire at the same time because the duration of the SPC is calculated by subtracting the filing date of the basic patent from the date of first marketing authorisation in the Community minus five years, with the maximum term being 5 years (plus a possible 6 month paediatric extension). Georgetown had been granted SPCs to various combinations of antigens, but wanted SPCs to the single antigens on the basis of the same patent, because the CJEU has previously ruled that an SPC for a single active ingredient can be infringed not only by a drug containing that ingredient, but also by a combination drug containing the ingredient. If they were not allowed to do that, they asked whether they could surrender their combination product SPCs in favour of the single product SPCs.

In the *Actavis Group v Sanofi* case, Sanofi's SPCs related to a combination of an antihypertensive agent (irbesartan) together with a diuretic (HCTZ). The patent claims included one directed to "irbesartan in combination with a diuretic", but nowhere in the claims or the patent description was HCTZ specifically recited. Sanofi had already been granted an SPC for irbesartan alone and was seeking an SPC for the combination with HCTZ on the basis of the same patent. The marketing authorisation for the combination with HCTZ was granted some time after that for irbesartan alone, such that the combination SPC would expire 14 months later than that to irbesartan alone.

In Georgetown, the CJEU decided that, it is possible, in principle, to obtain multiples SPCs for different products where a single patent protects a number of different products, provided that each of the products is protected as such by the basic patent.

Therefore, Georgetown should be allowed multiple SPCs for the single antigens and combinations of antigens that are protected as such by the same basic patent, with those SPCs all expiring on the same date.

If the marketing authorisation for the single active ingredient had been granted after a marketing authorisation for a combination of actives including that single active, it

seems that 2 SPCs could be granted on the basis of the same basic patent, 1 for the single active and 1 for the combination. However, those SPCs would both expire on the same date because the first marketing authorisation for the combination of actives, which contains that active, would be used to calculate the SPC duration, not the later marketing authorisation for the single active. The exception here would be where the active ingredient contained in the later marketing authorisation is different to that contained in the earlier marketing authorisation and both fall within the limits of protection conferred by the basic patent. In the Georgetown case, the HPV-16 antigen contained in the earlier marketing authorisation for Gardasil® is different to the HPV-16 antigen contained in the later marketing authorisation for Cervarix®, and both forms appear to be protected by the basic patent.

However, in the *Actavis Group v Sanofi* case, the CJEU outlined an exception to this principle, which arises in the situation of Sanofi's SPCs. Where a basic patent protects both a first active ingredient and a combination of that active ingredient together with another, and an SPC has already been granted for the first active ingredient on the basis of a relevant marketing authorisation, an SPC for the combination product cannot be obtained under the same basic patent on the basis of a later marketing authorisation.

The CJEU stated in the decision that a new SPC, potentially for a longer period of protection, cannot be obtained each time a medicinal product containing the principle active ingredient, protected as such by the basic patent and constituting the core inventive advance of that patent, is placed on the market in combination with another active ingredient which is not protected as such by that patent.

Therefore, Sanofi should not be allowed a combination SPC as they already have a single active SPC under the basic patent. Thus, Sanofi cannot benefit from the additional 14 months of protection afforded by the later marketing authorisation for the combination. Instead, the SPC for the single active covers the single active product and combination product under the one SPC, but expires on the earlier date.

At first, it may appear possible to circumvent this issue by filing separate patents (e.g. divisionals) to new active ingredients and related combination products. However, the CJEU specifically stated that each separate patent can only confer entitlement to a new SPC insofar as it covers "a totally separate innovation".

The CJEU failed to define what they meant by "totally separate innovation", so it will be up to the national Patent Offices and Courts to determine this.

Following those decisions, in *Actavis v Boehringer* (C-577/13), the CJEU was asked whether a patentee who has an SPC for a single active ingredient can have a second SPC to a combination product containing that active.

The CJEU was also asked whether it was allowable to amend the basic patent after grant, for example, to add a claim to specifically identify all active ingredients in an authorised combination product. This is an important point, because it is one way to address the issue of a claim not relating "implicitly but necessarily and specifically" to a combination
product. Thus, clarity as to whether this practice is allowable is much needed.

In this case, Boehringer obtained an SPC for telmisartan, and based on the same basic patent, subsequently sought an SPC for a later authorised product comprising telmisartan and hydrochlorothiazide. Boehringer were trying to obtain the combination SPC because that SPC would expire 4 years later than the SPC for telmisartan (due to the later issuance of the MA for the combination).

The situation was largely similar to the Actavis Group v Sanofi case mentioned above, where the CJEU had held that the combination product SPC should not be granted where the "core inventive advance" of the patent i.e. the single active ingredient, had already been the subject of an SPC, particularly when the combination product SPC had a later expiry date.

The CJEU's view on the first issue was consistent with the *Actavis Group v Sanofi* case in that they found that where a basic patent includes a claim to a product comprising an active ingredient which constitutes the sole subject-matter of the invention, for which the patentee has already obtained an SPC, and a further claim to a combination product, a second SPC is not allowed for the combination.

The CJEU noted that it was common ground that in the combination, telmisartan constituted the sole subject-matter of the invention and that Boehringer had not contributed to the discovery of hydrochlorothiazide. It seems the parties agreed this to be the case. Thus, it is not surprising that the CJEU came to this conclusion on what constituted the "innovation" in this case.

However, the concept of the "subject matter of the invention" remains difficult to apply where the parties have not agreed what constitutes the subject-matter of the invention. As mentioned above, it will be up to the national Patent Offices and Courts to determine this.

It is also not clear whether the situation would be different if a divisional application had been filed to the combination and the SPC pursued on that divisional

application. It is unlikely that it would have in view of the CJEU's findings in Actavis Group v Sanofi case (see above), where CJEU specifically stated that each separate patent can only confer
entitlement to a new SPC insofar as it covers "a totally separate innovation". Thus, it seems likely that a divisional application would not change the position and would not be needed if the combination product convincingly relates to a totally separate innovation to the single active product.

The second issue regarding post-grant amendment was unfortunately not answered by the CJEU in view of its negative decision on the first issue. It is likely that this issue will be referred to the CJEU again.

Is an adjuvant an active ingredient?

In the *Glaxosmithkline* case, the CJEU decided that adjuvants do not fall within the definition of "active ingredients" and so cannot be the product of an SPC.

This is the case even if the adjuvant influences the therapeutic effect of an active ingredient, because the adjuvant has no therapeutic effect on its own and so cannot be the subject of an SPC either alone or in conjunction with an active ingredient, such as an antigen.

Conclusions

The CJEU answered the issues based on the particular factual scenarios in which the references were made, making it difficult to draw out principles that can be applied more generally.

What we can determine from the decisions is that, active ingredients claimed in functional terms rather than purely structural terms, particularly antibodies defined by their binding to a particular antigen, should be sufficient for the purposes of SPC protection. More clarity is still needed on what is meant by "implicitly but necessarily and specifically" in terms of active ingredients other than antibodies, which are defined functionally.

Adjuvants are not considered active ingredients and so cannot be the product of an SPC.

With the exception of certain circumstances, such as Sanofi's combination SPC, multiple SPCs for different products should be possible on the basis of a single patent. However, a decision on whether those multiple SPCs are worthwhile needs to be balanced with a determination of the SPC term. For example, where the patent protects A and A + B, the SPC term for SPCs to A and A + B will be the same if the

first marketing authorisation encompasses A + B (e.g. A + B, A + B + C, etc.). In terms of infringement, the SPC for A can be infringed not only by a drug containing A, but also by a combination drug containing the ingredient, such as A + B. Thus in that situation, 2 SPCs may not be necessary. If the first marketing authorisation is only for product A, and the combination product A + B is later authorised, an SPC for A + B with a laterexpiry date seems to only be possible if the SPC applicant can convince the patent office that A + B is a "totally separate innovation" to A alone.

The Georgetowndecision provides some relief for SPC owners who, in situations like those in Georgetown, will not need to forfeit second and subsequent SPCs on the same basic patent.

In terms of SPC strategy, it is still difficult for SPC holders to formulate a strategy that deals with the increasingly confusing SPC decisions coming from the CJEU. One point that is clear is that patentees should aim to include claims to combinations on a general level, along with increasing levels of specificity before grant. Any likely commercial combination products should specified in as much detail as possible in the dependent claims so that the national patent offices do not struggle to determine if the combination is "implicitly but necessarily and specifically" claimed.