Patent Focus

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Strategic use of supplementary protection certificates (Part 1)

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INTRODUCTION

For many years I have observed the filing of Supplementary Protection Certificates (SPCs) on patents protecting pharmaceutical products, only to discover more and more uncertainties and irregularities in regard to interpretation of the Council Regulation (EEC) No 1768/92 that forms the basis of this additional patent term intended to compensate (to some degree) a patentee for delays in commercialising a product due to regulatory approval.

This paper is the first in a series, which is not intended to represent a legal review of the SPC Regulation, but more of an observational summary of how the system is being used by the pharmaceutical industry. However, it will be necessary to refer back to the SPC Regulation in order to draw some parallels between plain reading of the text, and the interpretation of the text by EU member states in determining the right of an application to result in the grant of a SPC.

Given that over 11 000 SPC applications have been filed worldwide, a comprehensive review would take considerable effort, so examples have been drawn from appropriate data sources to represent some of the SPC filing activities that occur. This study is not necessarily intended to suggest widespread occurrence of such activities, or that any one member state's patent office is interpreting the regulation incorrectly.

This first paper will review perhaps the most common belief of the SPC system, that the patent owner or product license holder only has one 'bite of the cherry' per product to gain a patent term extension. Article 3, specifically Sections (c) and (d), is the part of the SPC Regulation that deals with this.

> 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 authorization to place the product on the market as a medicinal product has been granted in accordance with Directive 65/65/EEC or Directive 81/851/EEC, as appropriate;
> (c) the product has not already been the subject of a certificate;
> (d) the authorization referred to in (b) is the first authorization to place the product on the market as a medicinal product.

In order to interpret Article 3(c), the term 'product' is defined in Article 1(b) as meaning *the active ingredient or combination of active ingredients of a medicinal product.*

Based on simple reading of the regulation one could therefore be forgiven for assuming that only one SPC can be granted for each active ingredient or combination of active

ingredients contained in a medicinal product. Taking a common-sense approach to the term 'active ingredient', one could further make the assumption that this should be defined by the International Nonproprietary Name (INN) assigned to that active ingredient (including any pharmaceutical forms thereof) by the World Health Organization. The data presented in this paper will challenge these assumptions.

Using the UK Intellectual Property Office (UKIPO) as an example, a review of SPC applications shows that multiple applications have currently been received in regard to 94 different 'products', when defined by the INN. For one particular INN, Human Papillomavirus (HPV) Vaccine, 33 separate applications for SPCs had been received by the UKIPO as of January 2009, from eight patentees, based on 11 different patents and each citing one of two marketing authorisations for products containing essentially the same active ingredient. Similar numbers of SPC applications had been received by most other EU member states.

The Grant of a SPC is not an automatic process, but instead undergoes a verification process by the national patent office that received the application, that it meets the criteria set out in the SPC Regulation. However, in a large number of cases these criteria are subject to national interpretation by each member state. In other cases, the interpretation is clarified by the European Court of Justice (ECJ) at least in the verification of SPCs from that point forward. The inevitable result is non-harmonised patent protection of pharmaceutical products across the EU and often widespread confusion in regards to validity and infringement issues, clearly not the harmonisation that the SPC Regulation was intended to provide (*see for example, Recital 6 to Regulation 1768/92*).

Applying the above assumptions to the HPV Vaccine SPC applications, one would not expect all of them to result in the grant of an SPC in a single country; in fact, we would expect that only one SPC would be granted. However, a review of SPCs that have been granted in the past by the UKIPO might suggest otherwise.

Taking the analysis of UK SPCs further, of the 94 INNs with multiple SPC applications, multiple certificates are *granted* in 28 cases (Table 1), seven cases having three granted certificates and two cases having four granted certificates. In three such cases each granted SPC for the INN has now expired.

Analysis of these examples shows that there is a range of circumstances giving rise to the grant of multiple SPCs in the United Kingdom (Table 2). Each circumstance is discussed below.

Same basic patent, same marketing authorisation

In this circumstance the expiry date of each SPC will be the same, as the dates used in this calculation are the same. Given the inevitability of this result, is there a reason for such SPC filing activity? The only case to draw from here relates to the Rotavirus

Table 1: INNs with multiple SPCs granted by UKIPO

ADALIMUMAB	HYALURONIC ACID	ROTAVIRUS VACCINE
BEVACIZUMAB	INSULIN ASPART	SELAMECTIN
BORDETELLA PERTUSSIS VACCINE	INSULIN GLARGINE	TASONERMIN
CEFTIOFUR	MOROCTOCOG ALFA	TRASTUZUMAB
CLOFARABINE	MYCOPHENOLIC ACID	VALGANCICLOVIR
DOXORUBICIN	NATEGLINIDE	HEPATITIS B VACCINE[a]
DULOXETINE	OMALIZUMAB	LEUPRORELIN[a]
EQUINE INFLUENZA VACCINE	PALIFERMIN	OMEPRAZOLE[a]
ETANERCEPT	RIVASTIGMINE	
GADOXETIC ACID	ROSIGLITAZONE	

[a]SPCs have expired.

Table 2: Circumstances giving rise to the grant of multiple SPCs in the United Kingdom

Basic patent	*Marketing authorisation*
Same	Same
Same	Different
Different	Different
Different	Same

vaccine 'Rotaschield', where each of three SPCs relates to different serotypes contained in the approved vaccine. Although this particular Marketing Authorisation (MA) has been withdrawn, the filing of three SPCs may have been to establish a defensive position against a situation where the validity of the basic patent were challenged, resulting in one or more of the serotypes not being protected by the basic patent and thus removing the eligibility for a SPC based thereon. In terms of the eligibility for grant of the three SPCs, it could be argued that each serotype was, in fact, a separate active ingredient that is, the vaccine was a combination of active ingredients, each of which was protected by the basic patent.

Same basic patent different marketing authorisation

In the pharmaceutical field, the patenting of generic structural formulae for small molecules and of platform technologies for biological products results in many situations where a patent can protect multiple active ingredients. In most cases, the different active ingredients are distinct enough to be assigned an individual INN and so it seems fair that more than one SPC is available on a single basic patent, providing the active ingredient in each cited MA is different. However, it is sometimes not clear what constitutes a different active ingredient or 'product' in interpreting the SPC Regulation and applying the test of whether the MA referred to is the 'first authorization to place the product on the market as a medicinal product'. This is one of the reasons why more than one SPC might be granted for a given INN in the United Kingdom, resulting in a later expiring SPC for at least one of the 'products' protected by the basic patent.

In two such cases, Hyaluronic Acid (Synvisc and Hylaform) and Hepatitis B Vaccine (HB-Vax and Engerix B), the active ingredients in each pair have similar chemical compositions but the actual active ingredients vary due to the process used to prepare the specific macromolecular compounds. It recognised that two separate sets of clinical trials were necessary to achieve the separate marketing authorisations cited in these cases, thus the cited MAs could be construed to relate to different active ingredients and the grant of the SPC would then be justified.

In the case of Equine Influenza Virus, two SPCs have been granted which cite the same marketing authorisation number (for both the community and the UK MA), yet they provide different authorisation dates on which the SPC is to be calculated. In this case it is possible that the later SPC relates to a variation of the original authorised product requiring only limited regulatory approval time, and so is not deserving of a separate term of protection.

Small molecules often provide more clear-cut examples. In the case of Omeprazole the marketing authorisation for the oral dosage form (containing the base compound) and the injectable dosage form (containing the Omeprazole sodium salt) were cited as the basis for the grant of two SPCs, the latter extending the life of the injectable product 7 months beyond that of the oral dosage form.

It should be noted at this stage (as highlighted in a recent ECJ decision[1]) that Point 11 of the Explanatory Memorandum to the Proposal for a Council Regulation (EEC), of 11 April 1990, concerning the creation of a SPC for medicinal products (COM(90) 101 final) specifies:

> Only one [SPC] may be granted for any one product, a product being understood to mean an active substance in the strict sense. Minor changes to the medical product such

> as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the issue of a new [SPC].

It is therefore expected that the grant of multiple SPCs on a similar basis to the Omeprazole case would not occur very often and, if it should, is likely to result in SPCs with questionable validity.

The term 'product' has been the subject of several, more in-depth legal reviews and judgements,[2,3,4] the scope of which is beyond the purpose of this paper. However, noteworthy is the UK Patents Court decision that authorisation to place a medicinal product containing a racemate on the market cannot be considered an authorisation to place a single enantiomer on the market.[5]

Different basic patents, different marketing authorisations

Naturally the SPCs granted under these circumstances would be unlikely to have the same expiry dates, so there is clearly a benefit to the patentee in extension of the monopoly of the product (or an aspect thereof) for which the later marketing authorisation was obtained.

Similar arguments exist to those presented in the above circumstance, where the products of the cited marketing authorisation contain different active ingredients, but share an INN simply because of the limitations of the INN system. Rotavirus Vaccine and Equine Influenza Vaccine (which fall into multiple categories in this study because three SPCs have been granted) are again examples where biotech products ask questions of the SPC Regulation because of variants produced by different production methods. However, the outcome here would appear to be fair.

In granting a second SPC in respect of products containing Insulin Aspart, the UKIPO considered the protamine form (essentially a longer acting crystalline form of Insulin Aspart) to be a different active ingredient to the previously authorised soluble form, thus extending the monopoly life of the latter product to nearly 4 years beyond that of the Insulin Aspart *per se*.

Similar situations exist in the cases of Doxorubicin, having citrate and sulfate salts as active ingredients in the respective cited MAs, and Mycophenolic acid sodium versus the Mofetil ester prodrug of Mycophenolic acid, cited in the MA for the second SPC. Ceftiofur is another example where SPCs were granted in the United Kingdom citing the sodium salt, hydrochloride salt and free base forms approved in three separate MAs.

It would be fair to say that the grant of secondary SPCs for some of these INNs constitutes a 'second bite of the cherry' in terms of extending monopoly protection of products containing them, and that this situation conflicts with the Explanatory Memorandum referred to in proposing the SPC regulation. It could also be argued that Article 3, Section (d) of the SPC Regulation is being interpreted incorrectly for some of these cases, because the later SPCs refer to marketing authorisation that are not the first to place the 'product' on the market. However, it is noted that with complex pharmaceutical technology it can be difficult to draw a line between what is the same active ingredient as that which is the subject of a previous marketing authorisation and what is not, and that this difficulty is increasing with biotechnology-derived products.

Different basic patents, same marketing authorisation

In the circumstance where the same marketing authorisation is cited as the basis for an SPC on different basic patents, Article 3(d) of the SPC Regulation becomes moot and the focus is more on the fulfilling the other requirements for grant. In such cases there are two significant outcomes, depending on whether the monopoly protection of the authorised product is extended by virtue of the second granted SPC or not.

In cases where the monopoly period is *not* extended the later-expiring SPC, possibly with more limited scope of protection, provides the patentee with extra 'insurance' should the validity of the first basic patent be challenged. On the one hand, general molecule patents and platform patents are being attacked on the basis of insufficiency, whereas the more specific 'selection' patents are being attacked for lack of novelty and inventive step over the earlier basic patent (as well as insufficiency). Even if the monopoly period is not extended, there is a certain value in being granted a second SPC that takes the onus away from the patentee in being required to select the patent to be extended.

Examples of INNs falling within these circumstances are Doxorubicin, Hepatitis B Vaccine (both pairs), Selamectin, Etanercept and Trastuzumab.

Perhaps the most significant benefit occurs here when patents protecting a product are obtained by different companies and cross-licensed to each other, or just to the company who commercialised the product. In this case, each patentee can control their own affairs with respect to maximising their monopoly protection period (and royalty revenue), and do not need to rely on a third party to do so.

Regulation (EC) No 1610/96 (relating primarily to the creation of SPC for Plant Protection products) contains sections that are also valid, mutatis mutandis, for the interpretation of Council Regulation (EEC) No 1768/92. In particular, Article 3(2) confirms the allowance of multiple SPCs providing the patents are held by different entitities:

> The holder of more than one patent for the same product shall not be granted more than one certificate for that product. However, where two or more applications concerning the same product and emanating from two or more holders of different patents are pending, one certificate for this product may be issued to each of these holders.

This benefit was further recognised in an ECJ judgement handed down in 1997[6] (Biogen) which ordered:

> here a medicinal product is covered by several basic patents, the Regulation does not preclude the grant of a supplementary protection certificate to each holder of a basic patent.

The judgement confirms that it is possible for multiple SPCs to be granted based on a single marketing authorisation, provided they use different basic patents. Indeed each of the SPCs granted in relation to the above-mentioned INNs cite a basic patent with different holders, and were granted after this judgement.

In all but three of these cases there was no granted SPC in place at the time of the later SPC application, either because the multiple SPC applications were made simultaneously or in quick succession, or because there was an extended period between application and grant of the first SPCs filed for the INN (as long as 9 years in one case). In such cases, the criteria for grant in Article 3(c) appear to have been met because at the date of the application the product (having the same marketing authorisation) had already been the subject of a certificate.

However, to an observer the later granted SPC in respect of Selamectin, Etanercept and Trastuzumab may appear to be invalid because a SPC was already granted for the active ingredient when the second SPC, based on a different patent but citing the same MA, was applied for. In these cases, Recital 14 of Regulation (EC) No 1610/96 valid for the interpretation of Council Regulation (EEC) No 1768/92 may become important, even though the conditions for obtaining a certificate have not been met.

> (14) Whereas the issue of a certificate for a product consisting of an active substance does not prejudice the issue of other certificates for derivatives (salts and esters) of the substance, provided that the derivatives

are the subject of patents specifically covering them;

However, these cases are fairly benign when observed by the generics industry as they do not prevent generic competition for an extended period of time when compared to the earlier-granted SPCs, and so are unlikely to result in any challenges to this interpretation of the Regulation.

Cases where the monopoly on the authorised product is extended by virtue of the second granted SPC tend to attract more attention from the generics industry. Of this final group of 16 INNs, for each case where a second SPC was granted, there was no granted SPC in place at the time of the later SPC application. Again, when applying the SPC Regulation using its literal terms, the criteria for grant of these secondary SPCs appear to have been met.

Noteworthy is that in all but one of the cases, the patent holders for the two granted SPCs were registered as being different corporate entities, even though some belonged to the same corporate group and so their grant does not conflict with the judge's interpretation of the SPC Regulation in Biogen.

This situation has not occurred by coincidence; it is clearly a result of the enforcement of Article 3(2). However, in two particular cases, the proprietor of basic patents used in two SPC applications for the same product was registered as being the same company until shortly before applying for the pair of SPCs, at which stage one of the patents was reassigned to a third party. Following review and grant of the two SPCs to two different companies (in accordance with article 3(2)), the patent was then reassigned back to the original proprietor.

This type of activity, although not prevalent is clearly taking advantage of 'loopholes' to maximise SPC protection of certain products. Thus, it appears not to be in the interests of pharma companies to consolidate their patent portfolios under one patentee when seeking to maximise opportunities to extend monopoly periods for their products.

Thus, for holders of different basic patents there appears to be an opportunity to apply for and be granted multiple SPCs referencing a single marketing authorisation simply by:

(a) making sure the basic patents are held by different proprietors; and
(b) ensuring that the applications are filed in quick succession or, if not, that the grant of the first filed is delayed until the secondary applications have been filed.

Bordetella Pertussis Vaccine is the only case where the multiple SPCs granted do not meet these criteria, and so may be challenged by potential generic entrants in an attempt to shorten the life of the overall monopoly period for this product. Although no certificate had been granted at the time of the applications, the grant of more than one certificate to the holder of more than one patent for the same product seems to fall foul of the Regulation. Again, Recital 14 of Regulation (EC) No 1610/96 may come into play here, but in the complex case of biologics and platform technology it will be difficult to interpret.

CONCLUSIONS

This paper has shown that multiple applications can and do result in the grant of multiple SPCs for a given INN, and even for a given marketing authorisation, at least in the United Kingdom. The benefits of this outcome to patent holders are increased 'insurance' against basic patent validity challenges, better control over administration with respect to SPCs and maximisation of the monopoly term of a given product to prevent generic competition.

The main circumstances to allow multiple SPCs to be granted appear to be where:

(a) it can be successfully argued that the active ingredient in a later MA cited in an SPC application is different that contained in the MA cited in an earlier

application (subject to definition in the Explanatory Memorandum);

(b) there is no granted SPC at the date of application of later SPCs because applications for all SPCs are made in close succession and/or, grant of earlier SPC is delayed *and* at the time of application and grant of the certificate, the proprietors of the basic patents are different.

Given the allowability of multiple SPCs using current interpretation of the SPC Regulation, the question of what constitutes a 'basic patent' becomes increasingly important as well as the clarification of what scope of protection a later-expiring SPC might have. This will ensure that the regulation is not used by patentees to unfairly extend the monopoly protection of their patented products, and is something that will be discussed in a later paper.

Referring back to the UK HPV Vaccine SPC applications, based on the initial assumptions, one would not expect all of these applications to result in the grant of an SPC in the United Kingdom; in fact we would expect that only one SPC would be granted. However, the fact that all of the SPC applications for HPV products have been made before any SPC citing the MA has been granted does not preclude the grant of any. Certainly, the grant of SPCs on multiple basic patents is also not precluded, providing the patent holders are different. It could also be argued that the active ingredients in the two cited MAs are not the same and so comply with Article 3(d) of the Regulation. There are obviously different considerations not discussed in this paper in determining which (if any) of these 33 SPC applications will be granted, but in answering the question of whether more than one SPC could be granted in relation to a single INN, the answer is a resounding 'Yes'.

One possible solution to make the SPC system fairer may be the implementation of an automatic selection process managed at the national patent office level, where upon grant of multiple SPCs citing the same marketing authorisation, the patent holder must select the SPC to remain in force and allow the others to lapse. Of course the practical working of this process where several distinct patent holders exist would be impossible, but certainly where the patent holders are within the same corporate group the possibility exists and would add more fairness to the implementation of the SPC Regulation as it currently stands.

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