Review of Supplementary Protection Certificate (SPC) decisions – Part 1

There have been several interesting developments in the world of SPCs since our 2023 Summer Review. As always, these provide plenty of room for thought-provoking debate. This first part of our review for 2024 deals with the recently issued opinion of the Advocate General in joint cases C-119/22 and C-149/22. This opinion represents the latest chapter in the long-running saga concerning SPCs for combination products. On a similar topic but moving closer to home, we discuss a recent Court of Appeal decision dealing with SPCs for so-called 'loose combinations', where obtaining protection represents a challenge for applicants. We then provide an update on the application of *Forsgren* across Europe, and how this decision is used to assess the fundamental question of whether something is an 'active ingredient' for SPC purposes. This edition ends with another look at the European Parliament's proposed reforms to the SPC legislation.

The second part of our review, which will be published in the September edition, discusses recent news from the CJEU concerning the application of Article 3(d). Next, we provide an update on the application of article 3(a) following Royalty Pharma, as well as Merck Serono's attempts to overturn Santen in post-Brexit UK. Finally, we will discuss the proposed reforms to the regulatory exclusivity system, which dovetail with SPCs and provide vital exclusivity for innovative pharmaceuticals.

We hope that our 2024 Summer Review provides a helpful and interesting overview of the key SPC developments from the last 12 months.

Daniel Wise (Partner), and Fergus Tyrrell (Senior Associate)

Combinations of active ingredients, legal provisions, and pending referrals

Advocate General weighs in on the allowability of combination SPCs.
By Fergus Tyrrell (Fellow)

Readers of our 2022 and 2023 Summer Reviews will be aware of the pending CJEU referrals concerning SPCs for combination products. After significant delays, the opinion of Advocate General Emiliou was issued on 6 June 2024. This long-awaited opinion echoed many familiar policy arguments, but suggested interpretations of both articles 3(a) and 3(c) of the SPC Regulation which will strike many as being at odds with current practice.

Background

Articles 3(a) and 3(c) following *Actavis I* (C-443/12), *Actavis II* (C-577/13), *Teva* (C-121/17), and *Royalty Pharma* (C-650/17)

Actavis I and *Actavis II* concerned situations that occur fairly regularly. A pharmaceutical company obtains a patent claiming a new and inventive active substance per se, as well as combinations of that new active substance with known active substances. A first marketing authorisation directed to this new active ingredient as a monotherapy is obtained, and an SPC for the new active ingredient (a 'mono-SPC') is obtained based on the patent. Subsequently, a second marketing authorisation directed to this new active ingredient in combination with another, known active ingredient is obtained. A second SPC (so-called 'combo-SPC') based on the (same) patent and this second MA would offer valuable additional exclusivity and potentially delay generic market entry. Unsurprisingly, these types of combo-SPCs have been extensively litigated in the national courts and before the CJEU.

In *Actavis I*, Sanofi held a patent and a mono-SPC for the new and inventive active ingredient ibersartan, which was the sole active ingredient in the medicinal product Aprovel. Sanofi issued a subsequent approval for CoAprovel – a combination product containing ibersartan and hydrochlorothiazide (HCT, a drug first discovered in the 1950s) – and sought a combo-SPC for ibersartan and HCT based on the same patent as the mono-SPC. The CJEU held, in essence, that the 'product' to which an SPC relates should be that which embodies the 'core inventive advance' of the basic patent, which in this case was ibersartan per se rather than the combination with HCT. As this 'core inventive advance' had already been the subject of the earlier mono-SPC, the subsequent combo-SPC was held invalid under article 3(c) of the SPC Regulation. Interestingly though, the CJEU's judgment emphasised that HCT was 'not protected as such' by the basic patent, potentially implying that the situation may have been different had the basic patent's claims been drafted differently.

The relevant facts of *Actavis II* were similar to those of *Actavis I*, and thus the CJEU's reasoning was similar to that given in *Actavis I* (although the wording 'sole subject matter of the invention' was preferred to 'core inventive advance'). However, the CJEU's ruling explicitly held that, as well as article 3(c), article 3(a) also precluded the grant of a later combo-SPC when an earlier mono-SPC has been granted on the basis of the same patent in respect of the 'sole subject matter of the invention'.

Following these two CJEU decisions, it was widely thought that the 'core inventive advance'/'sole subject matter of the invention' tests were relevant for assessing compliance with both articles 3(c) and 3(a). However, following later decisions *Teva* and *Royalty Pharma*, many believed that these tests were not relevant (or no longer relevant) to the assessment of article 3(a). In particular, the CJEU in *Teva* held that article 3(a):

> 'must be interpreted as meaning that a product composed of several active ingredients with a combined effect is "protected by a basic patent in force" within the meaning of [article 3(a)] where, **even if the combination of active ingredients of which that product is composed is not expressly mentioned in the claims of the basic patent, those claims relate necessarily and specifically to that combination. For that purpose**, from the point of view of a person skilled in the art and on the basis of the prior art at the filing date or priority date of the basic patent:
>
> - the combination of those active ingredients must necessarily, in the light of the description and drawings of that patent, fall under the invention covered by that patent; and

- each of those active ingredients must be specifically identifiable, in the light of all the information disclosed by that patent' [emphasis added].

In *Royalty Pharma*, the CJEU stated that, in coming to its decision in *Teva*, the court had 'clearly relied on an interpretation of article 3(a)… in the context of which the concept of "core inventive advance" is **not relevant**' [emphasis added].

The apparent rejection of the 'core inventive advance'/'sole subject matter of the invention' tests in the context of article 3(a) led some to question the relevance of the earlier *Actavis I* and *Actavis II* decisions and their applicability to article 3(c).

Joint cases *Teva II* (C-119/22) and *MSD* (C-149/22)

After conflicting national judgments concerning articles 3(a) and (c) in the context of combo-SPCs, both the Finnish and Irish courts referred questions to the CJEU (*Teva II* and *MSD*, respectively), as reported in our 2022 and 2023 Summer Reviews. The questions referred by the national courts are given in full at the end of this article.

The facts which led to the Finnish referral (*Teva II*) were similar to those of *Actavis II*. Merck Sharpe & Dohme ('MSD') obtained a monoSPC directed to the drug sitagliptin on the basis of a monotherapy approval and EP 1 412 357 ('EP'357'). MSD then obtained a combo-SPC to sitagliptin and metformin (a drug known since the 1920s) based on the same patent but a subsequent approval. When the combo-SPC was challenged by Teva, the court felt that given the inconsistencies discussed above it was unable to rule on articles 3(c) and 3(a), so it referred questions to the CJEU. The Irish referral (*MSD*) also arose as part of a challenge to the validity of a combo-SPC based on EP 0 720 599 ('EP'599').

The Advocate General's opinion

Choosing to deal with article 3(c) first, the Advocate General ('A-G') noted the 'factual proximity' between the facts of the cases at hand and those of *Actavis I* and *Actavis II*. He expressed 'a great deal of sympathy for the pragmatic and teleological reasoning' of those decisions and agreed with the policy considerations expressed in them. However, he did not agree that the 'core inventive advance'/'sole subject matter of the invention' criteria should be applied to the assessment of article 3(c). In his view, following the literal wording of the SPC Regulation, as well as *Santen*, he found that 'Article 3(c)… is not open to such a purposive interpretation'. Further, in his opinion, tests established in *Actavis I* and *Actavis II* conflate article 3(a) with article 3(c), creating 'regrettable confusion'. He also noted that the *Actavis I* and *Actavis II* tests fail to guard against pharmaceutical companies obtaining SPCs for combinations which do not represent the 'core inventive advance'/'sole subject matter of the invention' because, even if this test is applied, article 3(c) can still be circumvented by assigning relevant patents to different entities within the same corporate group, following *Biogen* – C-181/95 (and, one assumes, AHP Manufacturing – C-482/07). Thus, he concluded that the court should endorse a straightforward and literal construction of article 3(c), and deal with the policy considerations expressed in *Actavis I* and *Actavis II* under article 3(a).

So far, so simple(ish). However, the opinion takes a more controversial turn when it moves to its discussion of article 3(a). In interpreting the *Teva* decision, the A-G argues that the two criteria mentioned in that decision, namely the requirements that:

- the combination of active ingredients must necessarily, in the light of the description and drawings of that patent, fall under the invention covered by that patent; and
- each of those active ingredients must be specifically identifiable, in the light of all the information disclosed by that patent

apply even when the combination of active ingredients is 'expressly mentioned in the claims of the basic patent'. This finding was at odds with MSD's argument that the above requirements were relevant only when the combination was not expressly mentioned in the claims of the basic patent (e.g., when the claim requires a specific drug in combination with another drug defined only by a functional definition). By applying article 3(a) in this way, which requires the product to fall under the invention covered by the patent, the A-G appears to take the view that this fulfils the policy goals referred to in *Actavis I* and *Actavis II* of ensuring that the SPC attaches itself to the 'core inventive advance' of the patent/'sole subject matter of the invention'.

Of course, many had thought that the use of the 'core inventive advance' test in assessing article 3(a) had been killed off by the CJEU in *Royalty Pharma*. However, the A-G opined that the CJEU's comments on this point in *Royalty Pharma* are more semantic than substantive and argued that the court rejected the terminology used in the test (core inventive advance), and not the substance of it (the invention covered by the patent).

Also of note are the A-G's comments on how the 'specifically identifiable' requirement should be assessed. The A-G proposes what, on its face, appears to be an extremely strict test, namely one which requires 'patent practitioners [to] ask themselves a familiar question: could the basic patent be limited, via an amendment, to such a 'product' without breaching article 123(2) of the EPC? If not, that 'product' is not eligible for an SPC under article 3(a) of the SPC Regulation either.'

The opinion does acknowledge that combination SPCs should be allowable in certain circumstances, such as when there is a synergistic effect associated with the combination and where this combination is 'is the subject matter of a dedicated patent'. The A-G does, however, seem to argue for a restrictive approach in the allowability of using post-filed

data to support the existence of an advantageous effect associated with the combination ('The fact that, after the filing of the patent application, further research provided the safety and usefulness of the… combination should not be taken into account.').

Proposed answers to the referred questions

'(1) Article 3(a)… must be interpreted as meaning that to be regarded as "protected by a basic patent" within the meaning of that provision, a "product" must not only (i) be expressly mentioned or at least "specifically identifiable" in the claims but also (ii) fall under the invention which is the subject matter of that patent.

(2) Article 3(c)… must be interpreted as meaning that it does not preclude the grant of a supplementary protection certificate (SPC) for a combination of active ingredients where a previous SPC had been granted for one of those ingredients. The concepts of "core inventive advance" and "subject matter of the invention" are irrelevant for the purposes of the assessment of the condition laid down in that provision.'

Other developments around Europe

Sweden

Readers of the 2023 Summer Review will recall that there was the possibility of a third referral to the CJEU on SPCs for combination products from the Swedish Patent and Market Court. This case has a familiar fact pattern – AstraZeneca obtained a mono SPC on the basis of a monotherapy authorisation to dapagliflozin, and subsequently sought a combo-SPC on the basis of the same patent and a later authorisation for dapagliflozin in combination with metformin. However, this case has, perhaps unsurprisingly, been stayed by the Patent and Market Court pending the outcome of *Teva II* and *MSD*.

France

The French equivalents of the combo-SPCs at issue *Teva II* and *MSD* have been extensively litigated. The validity of the combo-SPC based on EP'357 was upheld during first instance proceedings, and *MSD* succeeded in obtaining a preliminary injunction against a generic manufacturer. In January 2024, the preliminary injunction was upheld by the Court of Appeal.

The combo-SPC based on EP'599 fared differently and was invalidated by the Court of Appeal after being upheld at first instance. This litigation is currently before the French Supreme Court, although proceedings have been stayed pending the issuance of the CJEU's decision.

Referred questions in *Teva II* (C119/22) from Finland

What criteria must be applied to determine when a product has not already been granted a supplementary protection certificate within the meaning of article 3(c) of Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products ('SPC Regulation')?

Must the assessment of the condition set out in article 3(c) of the SPC Regulation be regarded as being different from the assessment of the condition set out in article 3(a) of that regulation, and if so, in what way?

Must the statements on the interpretation of article 3(a) of the SPC Regulation in the judgments of the Court in Case C-121/17 and Case C-650/17 be regarded as relevant to the assessment of the condition in article 3(c) of the SPC Regulation and, if so, in what way? In that connection, particular attention should be paid to the statements made in those judgments regarding article 3(a) of the SPC Regulation, specifically:

- the essential meaning of patent claims; and
- the assessment of the case from the point of view of a person skilled in the art and in the light of the prior art at the filing date or priority date of the basic patent.

Are the concepts 'core inventive advance', 'central inventive step' and/or 'subject matter of the invention' of the basic patent relevant to the interpretation of article 3(c) of the SPC Regulation and, if any or all of those concepts are relevant, how are they to be understood for purposes of interpreting article 3(c) of the SPC Regulation? For the purposes of applying those concepts, does it make any difference whether the product in question consists of a single active ingredient ('mono-product') or a combination of active ingredients ('combination product') and, if so, in what way? How is the latter question to be assessed in a case in which the basic patent contains, on the one hand, a patent claim for a mono-product and, on the other hand, a patent claim for a combination product, the latter patent claim relating to a combination of active ingredients consisting of the active ingredient of the mono-product plus one or more active ingredients from the known prior art?

Switzerland

SPCs in Switzerland are based on Swiss national law, as Switzerland is outside the EU and thus is not bound by the SPC Regulation or the case law of the CJEU. As a result, the approach of the Swiss patent office and the courts sometimes differs to that taken in the rest of Europe.

MSD's combo-SPC based on EP'357 was upheld by the Swiss Federal Patent Court, which also granted a preliminary injunction against a generic manufacturer. A key question in this dispute was whether the MA for the combination product represented the 'first authorisation' within the meaning of article 140b, paragraph 2 of the Swiss Patent Act (which is analogous to article 3(d) of the SPC Regulation). The generic manufacturer argued, inter alia, that the combination of drugs at issue in the combo-SPC (sitagliptin and metformin) was not associated with an additional inventive advance vis-à-vis sitagliptin monotherapy, seemingly following the logic of the *Actavis* decisions discussed above. However, the court found that this was not relevant to the dispute at hand. That said, the court did note that the facts of the Swiss case differed from the corresponding cases elsewhere in Europe, as in Switzerland the combo-SPC was granted before the mono SPC to sitagliptin per se.

Conclusions

The A-G's opinion is, of course, not binding on the CJEU, and one can only speculate as to how much (if at all) the opinion will be reflected in the court's judgment. It will be interesting to see whether the CJEU takes the A-G's advice to re-frame the article 3(a) test again even after *Teva* and *Royalty Pharma* and adopt a literal interpretation of article 3(c). However, as the A-G does appear to concede that his suggestions merely fulfil the policy goals of the existing case law in a different way, the CJEU may decide to take a pragmatic approach and stick with the already-established tests if they believe that they achieve the aims of the SPC Regulation.

What does seem likely is that, over ten years after *Actavis I*, we do not seem to be any closer to getting clarity on how articles 3(a) and 3(c) should be applied to combination SPCs. We await the court's judgment.

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Referred questions in *MSD* (C-149/22) from Ireland

(a) For the purpose of the grant of a supplementary protection certificate ('SPC'), and for the validity of that SPC in law, under article 3(a) of Regulation (EC) No 469/2009 concerning the SPC for medicinal products [2009] OJ L152/1, does it suffice that the product for which the SPC is granted is expressly identified in the patent claims, and covered by it; or is it necessary for the grant of an SPC that the patent holder, who has been granted a marketing authorisation, also demonstrate novelty or inventiveness or that the product falls within a narrower concept described as the invention covered by the patent?

(b) If the latter, the invention covered by the patent, what must be established by the patent holder and marketing authorisation holder to obtain a valid SPC?

Where, as in this case, the patent is for a particular drug, ezetimibe, and the claims in the patent teach that the application in human medicine may be for the use of that drug alone or in combination with another drug, here, simvastatin, a drug in the public domain, can an SPC be granted under article 3(a) of the Regulation only for a product comprising ezetimibe, a monotherapy, or can an SPC also be granted for any or all of the combination products identified in the claims in the patent?

Where a monotherapy, drug A, in this case ezetimibe, is granted an SPC, or any combination therapy is first granted an SPC for drugs A and B as a combination therapy, which are part of the claims in the patent, though only drug A is itself novel and thus patented, with other drugs being already known or in the public domain; is the grant of an SPC limited to the first marketing of either that monotherapy of drug A or that first combination therapy granted an SPC, A+B, so that, following that first grant, there cannot be a second or third grant of an SPC for the monotherapy or any combination therapy apart from that first combination granted an SPC?

If the claims of a patent cover both a single novel molecule and a combination of that molecule with an existing and known drug, perhaps in the public domain, or several such claims for a combination, does article 3(c) of the Regulation limit the grant of an SPC;

(a) only to the single molecule if marketed as a product;
(b) the first marketing of a product covered by the patent whether this is the monotherapy of the drug covered by the basic patent in force or the first combination therapy; or
(c) either (a) or (b) at the election of the patentee irrespective of the date of market authorisation?

And if any of the above, why?

The Court of Appeal takes a tight line on SPCs for loose combinations

In the UK, the IPO's refusal of Newron's UK SPC application for a loose combination of safinamide, levodopa and a PDI has been upheld by the Court of Appeal.
By Hannah Brown, Adam Ellwood and Paul Kaufman (Fellows).



Background

'Loose' combinations, that is, combination products in which the active ingredients are not formulated together as 'fixed' combinations but are formulated separately, are common and important ways of combining drugs. For example, loose combinations are often required for an antibody formulated in solution which is to be used with a small molecule drug in a tablet form. Another example of a loose combination is an add-on therapy, where an additional drug is given on top of an existing therapy. However, there has been considerable doubt about whether article 3(b) of the SPC Regulation, which requires 'a valid authorisation to place the product on the market as a medicinal product', is fulfilled for SPC applications directed to loose combinations.

For a typical SPC application directed towards a fixed combination, the 'product' protected by the basic patent under article 3(a) of the SPC regulation is usually the combination of active ingredients, and the same combination of active ingredients is usually the subject of the marketing authorisation for the medicinal product. Therefore, the assessment of article 3(b) is often straightforward.

In contrast, for loose combinations the 'product' protected by the basic patent under article 3(a) is sometimes considered to be a combination of active ingredients, e.g. where the 'invention' lies in combining the active ingredients. However, the marketing authorisation for loose combinations will often list only one of the active ingredients as a component of the authorised medicinal product, with the other active ingredient being referred to as part of an authorised use. A more nuanced situation then arises where there is a question mark over whether the marketing authorisation authorises the combination of active ingredients, i.e. the 'product' under article 3(a), or just a single active ingredient, to be placed on the market as a medicinal product. As a result, applicants often find themselves in a scenario where the 'product' under article 3(a) is a combination of active ingredients, but the 'product' authorised to be placed on the market is a single active ingredient, i.e. there is a mismatch, leading to an objection under article 3(b).

In recent judgment *Newron Pharmaceuticals v The Comptroller General of Patents* ([2024] EWCA Civ 128), the UK Court of Appeal investigated whether such loose combinations could be the subject of an SPC in view of article 3(b) when the 'product' - under article 3(a) - is a combination of active ingredients but the marketing authorisation defines only one part of the combination as an active ingredient in the medicinal product. Unfortunately for Newron, Birss LJ dismissed Newron's appeal, upholding the decision of the High Court and the hearing officer of the UK Intellectual Property Office ('IPO') to refuse its SPC application on the basis that the loose combination in question is not the subject of the relevant marketing authorisation.

Previous case law

An earlier decision from the UK High Court in Yeda UK1 related to a similar situation for a 'loose' combination of cetuximab and irinotecan. Here, the Type II authorisation relied upon for the SPC application to the combination listed cetuximab as the single active ingredient in the medicinal product, but referred to the use of cetuximab in conjunction with irinotecan as an authorised use in the clinical particulars section. In this case, Lewison LJ found that the single active ingredient cetuximab was clearly defined as the subject of the marketing authorisation, and not the combination. In particular, Lewison LJ dismissed

the references to irinotecan as being 'wholly insufficient to amount to a marketing authorisation for a product consisting of both cetuximab and irinotecan'. Lewison LJ stressed that, when deciding what the 'product' is in the sense of article 3(b), the focus should be put 'on what the product is, rather than what it does', such that 'the concept of "product" cannot include the therapeutic use of an active ingredient covered by a basic patent'.

There have also been several CJEU decisions providing guidance on how the term 'product' within the meaning of article 3 of the SPC regulation should be interpreted. The CJEU decision in Medeva (C-322/10) concerned the interpretation of article 3(b) in particular, in the context of multivalent vaccines. The CJEU decided that it was possible to obtain an SPC for an active ingredient (or combination of active ingredients) 'A' based on a marketing authorisation for A in combination with one or more additional active ingredients 'B'. Even though A – the 'product' protected by the basic patent under article 3(a) – was not identical to A+B – the 'product' that the marketing authorisation authorised to be placed on the market – this was not seen to be an issue under article 3(b).

Finally, the landmark CJEU decision in *Santen* (C-673/18) concerned the availability of SPCs based on new medical uses of a previously approved active ingredient. The CJEU stated that the term 'product' within the meaning of article 3(d) of the SPC Regulation 'is not dependent on the manner in which that product is used'.

Decision

The decision concerns Newron's SPC application for a loose combination of three active ingredients: safinamide, levodopa and a peripheral decarboxylase inhibitor ('PDI'). The marketing authorisation relied upon lists safinamide (Xadago®) as the sole active ingredient of the medicinal product and refers to the use of safinamide as an add-on therapy with levodopa and a PDI2 for the treatment of Parkinson's disease in the clinical particulars as the sole authorised use. It was undisputed that claim 1 of the basic patent related to the combination of three actives, and that the 'product' protected by the basic patent under article 3(a) was this combination: the key question, relating to article 3(b), was therefore whether the marketing authorisation authorised this combination of three active ingredients to be placed on the market as a medicinal product.

In the court's leading judgment, Birss LJ referred to the SPC regulation and the Explanatory Memorandum that preceded it, noting that the scheme intends to strike a balance between various interests, including those of pharmaceutical researchers, public health and generics. Birss LJ agreed with the Comptroller that the terms of the SPC regulation already strike this balance, so it is not 'a balancing exercise where courts are invited to undertake on a case-by-case basis'. Birss LJ also stressed that the SPC scheme is intended to be simple and transparent, and easy to apply by the patent offices.

It is against this backdrop that Birss LJ went on to apply a simple, and strict, 'orthodox' approach to determining the 'product' that was the subject of the marketing authorisation. Birss LJ proposed that the simple question to be answered to determine what amounts to the 'product' is: 'what is the active ingredient in the medicinal product authorised by a given marketing authorisation?' When answering this question, no account of a product's intended use is taken into account, meaning that active ingredients mentioned only in the context of a particular use of the medicinal product do not form part of the 'product' itself.

Birss LJ endorsed this approach by reference to a string of previous decisions taking the same line, starting with early cases such as *Pharmacia Italia SpA* (C-31/03), *MIT* (C-431/04) and *Yissum* (C-202/05), as well as later cases *Yeda UK* and most recently *Santen* (C-673/18).

Perhaps unsurprisingly, *Neurim* (C-130/11), in which the CJEU diverged from its previous case law and proposed that the use of a product should be taken into account, was dismissed by Birss LJ as having 'difficulties'. In particular, Birss LJ commented on Neurim's failure to address the early CJEU cases mentioned above, and the CJEU's later contradiction of its finding in *Santen*.

Birss LJ dismissed *Medeva*, in which the CJEU acknowledged that the requirements of article 3(b) are fulfilled where the 'product' under article 3(a) is A but the marketing authorisation authorises A+B to be placed on the market as a medicinal product, on the basis that it 'does not alter the law… from looking at the run of CJEU authority up to *Santen*'.

Applying these decisions to the facts at hand, Birss LJ agreed with the hearing officer and the High Court that safinamide alone was the subject of the marketing authorisation. This was on the basis that the Commission decision mentions safinamide only, and the medicinal product in the SmPC includes safinamide as the sole active ingredient. Levodopa, on the other hand, is listed only in the context of the therapeutic indication for safinamide, so was considered to be an aspect of how safinamide is used. Answering the simple question to be applied ('what is the active ingredient in the medicinal product authorised by a given marketing authorisation?'), Birss LJ noted that the relevant marketing authorisation authorises Newron to market safinamide alone, and it was undisputed that it does not authorise Newron to put on the market any other active ingredient.

Newron had sought permission to include expert evidence examining the marketing authorisation, since there were some references to levodopa and PDIs in the detailed annexes. This request was ultimately refused, and in any event Birss LJ noted that a 'minute analysis' of the lengthy documents associated with the marketing authorisation should not be necessary in answering the simple question above.

Finally, in relation to the 'balance' allegedly struck by the SPC scheme, Birss LJ commented that *Santen* makes clear that while the purpose of the SPC scheme is to support incentivising investment in research, 'not all kinds of inventions, deserving of patents though they all may be, will be able to obtain an SPC'.

In view of these findings, the Court ultimately decided that safinamide alone was the subject of the marketing authorisation, meaning that there was no valid authorisation under article 3(b) to place the undisputed 'product', i.e. the combination of three active ingredients, on the market.

Conclusion

The judgment in *Newron* confirms that, owing to the way in which courts tend to interpret the authorised product, obtaining SPCs for loose combinations is not straightforward.

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What does it take to be an 'active ingredient'?

Updates on the application of Forsgren across Europe on Halozyme's Herceptin Hylecta® and MabThera® SPC families. By Rhodri Hopes (Fellow), David Holland (Fellow).

Over the previous few years, we have been following the journey of two SPC families covering the marketed products Herceptin Hylecta® and MabThera®. The fate of the SPCs in both families turns on whether recombinant human hyaluronidase is an 'active ingredient' within the meaning of article 1(b) of the SPC Regulation. A complication for these SPCs is that the hyaluronidase is characterised as an excipient in the regulatory documents, so the SPC applicant Halozyme is having to rely on evidence outside of the regulatory documents in support of hyaluronidase being an 'active ingredient'. The leading case here is the CJEU's decision in *Forsgren* (C-631/13) and, as reported previously, there has been divergence between the national courts when applying this decision.

Since our 2023 article, two further decisions have issued around Europe: one from the UK IPO; and one from the French Court of Cassation (the French Supreme Court). Although both ended negatively for Halozyme, these decisions provide further guidance showing how *Forsgren* is being applied. Interestingly, some countries are open to considering evidence from outside the regulatory documents, whereas others refuse to consider such evidence, so the door for a CJEU referral remains open!

The importance of the 'active ingredient' and the 'product'?

SPCs are granted based on the first marketing authorisation for a 'product'. The 'product' is defined in article 1(b) as an 'active ingredient' or 'combination of active ingredients', neither of which is defined in the SPC Regulation. This means that a combination of 'active ingredients' that has not previously been approved together is treated as a new 'product', even if each component has previously been authorised separately. Therefore, when an applicant is seeking an SPC to a new product containing an 'active ingredient' that has previously been authorised, establishing that there is a second 'active ingredient' present in the new product can open the door to new SPC protection for the combination. The key question in these circumstances is what counts as an 'active ingredient'?

What is the 'active ingredient'? – *Forsgren*, *MIT*, and *GSK*

The first CJEU decision defining 'active ingredient' was *MIT* (C-431/04). The CJEU held that an 'active ingredient' in the context of article 1(b) must provide an effect of its own on the human or animal body. As such, an excipient that provided no effects was not an 'active ingredient'. The CJEU decided *GSK* (C-210/13) with similar reasoning, holding that an adjuvant that provides no therapeutic effects of its own is not an 'active ingredient', even though it may enhance the overall therapeutic effect of the vaccine.

Forsgren (C-631/13) was the next decision from the CJEU on this point. The underlying case concerned the Synflorix® vaccine that was approved for 'active immunisation against invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae in infants and children from six weeks up to two years of age'. Synflorix® contains Protein D, which is conjugated to polysaccharide 'active ingredients'. Protein D had to be considered as an 'active ingredient' for the SPC to be granted, but the relevant regulatory documents described Protein D as a 'carrier protein' and not as an 'active ingredient'.

Protein D had two independent effects: (i) as a vaccine against a middle ear inflammation caused by Haemophilus influenzae bacteria; and (ii) as an adjuvant to enhance the substances effective against pneumococci (the pneumococcal polysaccharides). The referring court (the Austrian Court of Appeal) considered that the adjuvant effects were irrelevant in view of GSK, but

was unsure whether the immunogenic effects against Haemophilus influenzae meant that Protein D should be considered as an 'active ingredient'. One reason for the Court's unease was that these immunogenic effects did not overlap with the approved indication for Synflorix®. The case was referred to the CJEU to clarify what constitutes an 'active ingredient'.

During the CJEU proceedings, the European Commission argued that the assessment of whether a component is an 'active ingredient' should be restricted to the regulatory documents that led to the marketing authorisation. The Commission argued that the SPC system was 'intended to establish some simplicity and some transparency' and that '[t]hat objective would not be achieved if the competent authority were required to verify by reference to sources other than the marketing authorisation whether the substance at issue is an active ingredient.' The CJEU did not follow this, and instead held that

> 'a carrier protein conjugated with a polysaccharide antigen by means of a covalent binding may be categorised as an "active ingredient" within the meaning of that provision **only if it is established that it produces a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indications of the marketing authorisation**, a matter which it is for the referring court to determine, **in the light of all the facts of the dispute in the main proceedings**.'

Although the CJEU's decision in *Forsgren* reinforces its earlier decisions in *MIT* and *GSK* that each 'active ingredient' must provide its own specific effect (i.e. its own pharmacological, immunological or metabolic action that is covered by the therapeutic indications of the marketing authorisation), it states that this assessment should be made 'in light of all the facts'. Referring to facts outside of the marketing authorisation potentially provides applicants with a wide range of options when arguing for SPC protection.

Halozyme's Herceptin Hylecta® and MabThera® SPC families

Halozyme has two families of SPC applications that have generated litigation in the European national courts over the past few years. The first SPC family is based on EPB2,163,643 and relates to the Herceptin Hylecta® product, which contains trastuzumab in combination with recombinant human hyaluronidase. The second SPC family is based on EPB2,405,015 and relates to the MabThera® product, which contains rituximab also in combination with hyaluronidase.

Separate marketing authorisations had granted for trastuzumab and rituximab as monotherapies many years before either of these two patents had been filed, which means that any SPCs based on those authorisations and patents would have had no positive term. Following these initial authorisations, authorisations for Herceptin Hylecta® and MabThera® were granted, which now included the hyaluronidase. The later date of these authorisations means SPCs based on these patents would have meaningful SPC term.

However, article 3(d) of the SPC Regulation requires that the marketing authorisation supporting the SPC application is the first authorisation to place the product on the market. In view of the monotherapy approvals, Halozyme had to argue that the 'product' authorised in the later authorisations was the combination of trastuzumab or rituximab with hyaluronidase, i.e., that the hyaluronidase is also an 'active ingredient'. If this argument was successful, then the later combination authorisations would have been the first for the new combination and the SPC applications may have been allowable. However, hyaluronidase is listed as an excipient on the regulatory documents that led to the relevant authorisations. As a result, various national patent offices refused Halozyme's SPC applications on the basis that only trastuzumab or rituximab could be the 'product', and therefore the SPC applications violated article 3(d) because of the earlier monotherapy approvals.

How do the new decisions from France and the UK apply *Forsgren*?

France

Readers of last year's article will know that the French Supreme Court upheld the Court of Appeal's refusal of the Herceptin Hylecta® SPC application (Court de Cassation appeal number 21-15.221). Although on its face this appeared to be a negative outcome for applicants in a similar situation to Halozyme, there was a glimmer of hope in the decision because the French Supreme Court was willing to consider evidence outside of the marketing authorisation when deciding whether a component is an 'active ingredient'. Indeed, when interpreting *Forsgren*, the Supreme Court held that

> 'when the Marketing Authorisation does not qualify a substance as an "active ingredient", it is **rebuttably presumed** that this substance does not produce its own pharmacological, immunological or metabolic effect covered by the therapeutic indications covered by this MA' [emphasis added].

Halozyme was unable to provide sufficient evidence to support recombinant human hyaluronidase being an 'active ingredient' under this test. Had it been able to do so, it may have been successful in getting the refusal overturned.

Since our 2023 article, the MabThera® SPC application has reached the French Supreme Court (Court de Cassation appeal number 2216.262). As with the Herceptin Hylecta® case, the Supreme Court was

considering whether the Court of Appeal was correct to uphold the patent office's refusal of the SPC application.

Unfortunately for Halozyme, the Supreme Court upheld the refusal for analogous reasoning to the Herceptin Hylecta® case. The Supreme Court repeated its view that when a component is listed outside of the 'active ingredient(s)' recited in the marketing authorisation, there is a rebuttable presumption that the component is not an 'active ingredient' for SPC purposes. The Supreme Court again held that the lower courts were correct to decide that hyaluronidase was an excipient rather than an 'active ingredient' (in line with the marketing authorisation) because no compelling evidence to the contrary had been adduced.

Although this is another negative result for Halozyme, innovators will be heartened to see that the French Supreme Court has reaffirmed its earlier decision that the assessment of whether a component is an 'active ingredient' should consider evidence outside of the marketing authorisation. In doing so, the current French approach seems to leave the door open for a component to be considered as an 'active ingredient' irrespective of how it is described in the regulatory documents.

Having said this, there is still little clarity on what quality of evidence may be required to overcome the 'rebuttable presumption' test that the French courts seem to have settled on. What does seem clear however, is that the French Supreme Court wants to see evidence related to the specifically approved indication, as opposed to evidence of a more general benefit associated with the component (in line with comments from the CJEU in *Forsgren*). Indeed, when considering Halozyme's evidence in the MabThera® case, the French Supreme Court held that:

> 'scientific documents produced by Halozyme to demonstrate a specific therapeutic effect of recombinant human hyaluronidase are insufficient to establish the existence of a **specific** pharmacological, immunological or metabolic effect in the treatment of non-Hodgkin's lymphoma' [emphasis added].

UK

In March 2024, the IPO refused both the Herceptin Hylecta® and Mabthera® SPC applications in one decision (IPO decision BL O/0257/24). Working through the relevant retained EU case law, in particular, *MIT*, *GSK*, and *Forsgren*, the hearing officer concluded that it was possible for evidence outside of the marketing authorisation to be considered when assessing whether a component was an active ingredient, but that to be convincing, the evidence had to be relevant to the specifically approved therapeutic indication. Analysing the various literature filed by Halozyme, the hearing officer noted that

> 'while these references indicate that hyaluronidase has properties that show it has potential to be used to treat cancer in general and that it is worth investigating further, it does not provide information on how hyaluronidase acts in the treatment of the specific cancers of interest, e.g., HER2 breast cancer or NHL, the specific treatments referred to by the respective MAs.'

Failure to provide such specific evidence led, in part, to the refusal.

However, in a further blow to Halozyme, and indeed to SPC applicants more generally, the hearing officer held that

> 'in order for a substance to be considered an active ingredient, **it is necessary that the marketing authorisation**, including the EPAR, **must contain, at the very least, some indication** that the substance gives rise to a pharmacological, immunological or metabolic effect of its own for the therapeutic indication covered by the MA' [emphasis added].

To meet this requirement, an SPC applicant would seemingly have to point to something positive in the marketing authorisation documents supporting that the component in question is an 'active ingredient'. This approach is clearly less applicant-friendly than the French Supreme Court's 'rebuttable presumption' test.

One particular aspect of the hearing officer's decision that is difficult to align with *Forsgren*, is the requirement that there must be something positive in the marketing authorisation supporting a component as an 'active ingredient'. In particular, the CJEU held that the assessment for whether a component is an 'active ingredient' is 'a matter which it is for the referring court to determine, in the light of all the facts of the dispute in the main proceedings'. Taking the hearing officer's reasoning forward, an SPC application would seemingly be refused if there was no indication of a component's pharmacological, immunological or metabolic effect in the marketing authorisation, even if there was compelling evidence outside of the marketing authorisation that the component contributed to the specifically approved therapeutic indication. In essence, an SPC application could be doomed to fail purely based on the content of the marketing authorisation. It is difficult to rationalise how this part of the hearing officer's test takes into account all the facts, following the CJEU's finding in *Forsgren*.

Halozyme has challenged the IPO's decision at the UK High Court (case number CH2024000108). Although Halozyme's arguments are not publicly available at the time of writing, we will be watching this case closely, and look forward to seeing how the High Court grapples with this important issue.

How do these new decisions fit in with those previously reported?

These two SPC families continue to provide useful insight into the diverging application of

Forsgren in the national courts. Summarising what we know so far from around Europe:

i. The French courts seem to take an applicant-friendly approach when interpreting *Forsgren* by considering evidence outside of the regulatory documents and being open to such evidence overruling the characterisation of a component in the regulatory documents. Readers of our previous articles on this topic will know that the Spanish courts are also willing to take outside evidence into account when determining the 'active ingredients' (see *High Court of Justice of Madrid, Appeal number* 256/2019).

ii. The French courts appear to have a strict view on the effect that an applicant can rely on – it must be specific to the approved indication. In both the Herceptin Hylecta® and MabThera® cases, the French courts did not consider that the applicant had cleared this hurdle with the evidence it put forward. In contrast, as discussed in previous articles, the Spanish courts considered and ultimately allowed the Herceptin Hylecta® SPC application (High Court of Justice of Madrid, Appeal number 256/2019). It is not clear whether these different outcomes have their roots in a different factual interpretation of the evidence put forward by Halozyme or a different application of *Forsgren*.

iii. The IPO requires that the marketing authorisation must contain some indication that the component contributes to the specifically approved indication. We await the view of the UK courts.

iv. The Swedish courts seem unwilling to take into account any evidence outside of the marketing authorisation, holding that 'there is no support for taking into account documentation other than that on which the sales approval was based in order to determine what constitutes the product according to the sales approval' in its assessment of the Herceptin Hylecta® case (see Swedish Court of Appeal decision PMÖÄ 12516-21).

Conclusion

There seems to be two particular points of divergence opening up between the national courts on the topic of identifying active ingredients for the purposes of SPC law. The first point is whether evidence outside of the marketing authorisation should be considered at all (Sweden thinks not, whereas Spain and France disagree), and if so, are there any conditions attached. The second point is whether it is a requirement that the effect relied upon is that of the specifically approved indication (as the French and UK tests seem to consider), or whether it can be a more general effect (as the Spanish courts held). In view of this divergence, we wonder whether any national court will consider referring questions to the CJEU for clarity on how *Forsgren* should be applied.

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European parliament approves new SPC regulations

Proposed reforms to the EU's SPC regulations pass the first legislative hurdle. By Oliver Williams (Student) and Paul Kaufman (Fellow)


In last year's review, we explored the European Commission's proposed reforms to SPC regulations. On 28 February 2024, the European Parliament approved the first round of proposals to reform EU SPC legislation, which introduce centralised examination and unitary SPCs.

These proposals are the European Commission's original proposed reforms with amendments from the European Parliament's Committee on Legal Affairs intended to clarify certain aspects of the legislation. Further amendments proposed by members of the European Parliament (MEPs) to remove the highly controversial pre-grant opposition procedure for new SPC applications were not adopted.

Introduction

Last year, we reported on the European Commission's proposed significant reforms to streamline the SPC regime. The main aim of the European Commission was to simplify certain aspects of the current SPC regime in which individual applications are filed at each national patent office (NPO) where SPC protection is sought. This national filing regime can lead to inconsistent outcomes across Europe and creates an administrative burden for applicants.

The European Commission's proposed reforms, which have now been adopted:

a. Introduce a centralised examination procedure for SPCs, and
b. Introduce a unitary SPC.

Under the reformed regime, the European Union Intellectual Property Office ('EUIPO') will centrally examine SPC applications that rely upon a European Patent (including a Unitary Patent, which gives rise to a unitary SPC) and a centralised marketing authorisation granted via the European Medicines Agency. After substantive examination, the EUIPO will issue an 'examination opinion' on whether the SPC should be granted, which may be positive, negative, or partly so. This examination opinion will be binding on NPOs, which will be obliged to grant or refuse the SPC application accordingly. In the pre-grant opposition procedure, third parties may file observations on the validity of an SPC application after the application has been published, and may oppose a positive (or partly positive) examination opinion.

Debate and vote in the European Parliament

At first reading on 28 February 2024, the European Parliament voted to approve the four new proposed SPC regulations proposed by the European Commission, with amendments proposed by the Committee on Legal Affairs (some of which are discussed below).

During the plenary debate, MEPs noted that the reforms will increase European harmonisation compared to the current fragmented regime. Several MEPs also highlighted that the reforms, including the centralised examination procedure and particularly the new unitary SPC, will reduce costs and excessive red tape for applicants.

Significant amendments rejected

The Parliament has rejected an amendment proposed by the European People's Party ('EPP') to delete provisions relating to the centralised pre-grant opposition procedure before the EUIPO. These provisions have attracted substantial criticism from innovators concerned that the pre-grant opposition system could be abused by third parties to cause significant delay to the examination process, e.g. to evade enforcement or to consume the practical SPC term. The Parliament's retention of the pre-grant opposition procedure will be seen by many as a missed opportunity to reduce uncertainty for innovators.

The EPP also proposed two further amendments to the unitary SPC regulations to delete provisions permitting declarations of invalidity to be granted by the EUIPO and provisions relating to counterclaims for invalidity. The aim of these amendments was to give the UPC sole competency to hear invalidity actions relating

to unitary SPCs, to provide consistency and to avoid SPC holders being faced with invalidity challenges at both the EUIPO and UPC. These amendments were also rejected, which arguably represents another missed opportunity to increase legal certainty.

Other amendments considered

The European Parliament adopted a suite of so-called 'compromise amendments' to the proposals, previously approved by the Parliament's Committee on Legal Affairs. Some of the key substantive changes, which have been introduced by these compromise amendments, are summarised below:

- **Definition of the term 'economically linked'** – The Commission's original legislative proposal prohibited 'economically linked' parties from obtaining multiple SPCs for the same product. This term has now been defined such that two parties, or 'holders', are economically linked if, 'in respect of different holders of two or more basic patents protecting the same product, that one holder, directly or indirectly through one or more intermediaries, controls, is controlled by or is under common control with another holder'. The definition brings some clarity but does not specify when in time the economic link is determined, so uncertainty remains regarding how, e.g., future mergers may affect SPC validity.
- **Product protected by the basic patent** – Proposed recital 8, which seems intended to clarify article 3(a), has been amended to clarify that the drawings of the patent must be taken into account alongside the claims and description, and that the patent must be assessed on the basis of the skilled person's common general knowledge and the prior art, at the filing or priority date. This wording, especially the reference to the prior art, now more closely reflects that of recent decisions from the CJEU on article 3(a) in C-121/17 *Teva* and C-650/17 *Royalty Pharma*.
- **SPCs for combinations and derivatives of protected products** – Proposed recital 9, which seems intended to clarify article 3(c), has been amended to state that the product for which an SPC is sought, or any derivative of that product, should not already have been the subject of a prior SPC (previously these recitals referred to 'therapeutically equivalent' derivatives). Unclear wording, which seemed to prohibit SPCs for combination products where one component had already been the subject of an SPC, has also been deleted from these recitals. This amendment is potentially in response to comments from the German Bundesrat alleging that this prohibition contradicted CJEU case law (e.g., in C-443/12 *Actavis*).
- **Disclosure of public financial support in application** – Applicants are required to supply 'any information on all direct public financial support received for research related to the development of the product for which the SPC is requested' in their application, and this information will be made available on the public register. From an initial review, the consequences of not supplying this information are unclear, and it seems that failure to provide this financial disclosure has not been added to the grounds for invalidity of an SPC.
- **Experience of EUIPO examination panels** – EUIPO SPC examination panels will include at least one member with at least five years' experience examining patents and SPCs, to address stakeholders' concerns that the EUIPO lacks expertise in SPC matters.
- **Acceleration of examination process** – Provisions have been introduced to accelerate examination in certain urgent situations (e.g., if expiry of the basic patent is imminent). In the expedited examination procedure, issuance of the first examination opinion is expedited from 6 months to four months after publication, and the window for third parties to file observations on the examination opinion is reduced from three months to six weeks. These changes may be insufficient to address stakeholders' concerns about malicious delaying tactics being employed by competitors while the pre-grant opposition procedure remains.
- **Opposition oral proceedings** – Opposition oral proceedings before the EUIPO will now be public, in contrast to the Commission's original proposal.

While these amendments aim to clarify certain aspects of the new proposals, key points of concern from stakeholders remain untouched by any proposed amendments to date, such as the lack of transitional provisions in the regulations, and uncertainty regarding how and when applicants should obtain consent for the grant of SPCs based on marketing authorisations held by third parties.

Next steps

The European Parliament's initial approval of new SPC legislation is a major step forward, but the future of the SPC regime is still uncertain. The amended proposals will now be considered by the Council of the EU (made up of ministers of national governments) and the European Commission. These bodies will take their own views on the proposals and could adopt their own amendments (including any amendments rejected by the Parliament), and so the ultimate legislative outcome remains uncertain. After negotiations between these institutions and further consultations, we expect that finalised proposals will be voted on again later this year. However, there is no time limit by which the Council must provide its views on the proposals, and such timing depends on political impetus from the Council Presidency.

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