From *Takeda* to *Teva v Merck*: Are We Treading the Right Path on Combination Product SPCs? (Part 2)

Dr Tony Rollins

Nicola Dagg

Steven Baldwin*

EU law; Patents; Pharmaceuticals; Supplementary protection certificates

In two earlier articles, including Part I of this series, we discussed the diminution of SPC term since SPCs were introduced in 1993, how the understanding of the definition of "product" in art. 1(b) of Regulation 469/2009 (the SPC Regulation) has developed over time and how various courts within Europe have dealt with the definition of product. In this article, we look in greater detail at the treatment of chemical combination products within the SPC system. In particular, we consider the key role that combination product cases have played in the development of the law regarding art.3(a) and 3(c) of the SPC Regulation. As part of that, we look at whether the CJEU should take the advice of Arnold J in the UK and adopt a "core inventive advance" test into SPC law. We set this discussion within the context of how pharmaceutical companies have applied for chemical combination products in practice since inception of the SPC Regulation and how the average SPC term for chemical combination products has dwindled over time.

In two earlier articles,[1] including Part 1 of this series, we discussed the diminution of the SPC term since SPCs were introduced in 1993, how the understanding of the definition of "product" in art.1(b) of Regulation 469/2009 (the SPC Regulation) has developed since the SPC Regulation came into force and how various courts within Europe (including the Court of Justice of the EU (CJEU)) have dealt with the definition of product.

In this piece, we look in greater detail at the treatment of chemical combination products within the SPC system.[2] In particular, we will consider the key role that combination product cases have played in the development of the law regarding art.3(a) and 3(c) of the SPC Regulation including the potential problems that have been caused by trying to adopt a "one size fits all" policy to the tests applicable to single and combination products. As part of that, we will look at whether the CJEU should take the advice of Arnold J and adopt a "core inventive advance" test into SPC law. This discussion will be set within the context of how pharmaceutical companies have applied for chemical combination products in practice since inception of the SPC Regulation and how the average SPC term for chemical combination products has dwindled over time.

The reduction in term for chemical combination SPCs

Dr Rollins has examined the patents on the UK Intellectual Property Office (UKIPO) register for the years 1994–2011[3] that relate to SPCs for chemical combination products.[4]

On the basis of this research we were able to calculate the term of the patent plus SPC protection from marketing authorisation to SPC expiry for the chemical combination SPCs granted within that period. With one or two exceptions (e.g. SPC/GB02/008 and SPC/GB08/022), the average term was 15 years for SPCs filed up to the end of 2008. Since then, however (which covers about 33 per cent of the SPCs reviewed), the situation has changed considerably and there were only two SPCs with a 15-year term from 2009 to the end of 2011. In fact the average term for combination SPCs granted from 2009 to the end of 2011 was about 10.6 years.

This suggests that more now needs to be done to provide innovative pharmaceutical companies with adequate compensation for the research and development (R & D) efforts they invest in developing chemical combination products.

The position on combination products when the SPC Regulation first came into effect

The SPC Regulation has provided for SPCs to be granted for combination products from its inception (as Regulation 1768/92) in January 1993. An early example that one of us was involved in is SPC/GB/93/090 (acrivastine/pseudoephedrine). In this case two SPCs had been filed based on the same basic patent, one to the new

* Dr Tony Rollins, (President of the Chartered Institute of Patent Attorneys (CIPA)); Nicola Dagg (Global Head of Intellectual Property, Allen & Overy LLP); Steven Baldwin (Senior Associate, International Intellectual Property Group, Allen & Overy LLP). Please note that the views expressed by Dr Rollins in this article do not necessarily represent the views of CIPA.

[1] T. Rollins, "How Europe's SPC regime works in practice" (2016) 260 M.I.P. 54, and (2017) 39 E.I.P.R. 555.

[2] The definition of "product" is set out in art.1(b) of the SPC Regulation which defines it as: "the active ingredient *or combination of active ingredients* of a medicinal product" (Emphasis added).

[3] 1993 was not included because this was the first year of operation of the SPC Regulation and transitional provisions were in place that could cause distortions for this year. 2012 and onwards were not included because there were still a large number of pending SPC applications for these years at the time that the work was carried out.

[4] In performing this analysis it was necessary for Dr Rollins to exclude various types of SPCs on the register. As a first step, he ruled out of consideration SPCs that relate to agrochemical, veterinary or imaging agents and also SPCs that have not yet been granted, or have been rejected or withdrawn. He then excluded biological/peptide SPCs.

chemical entity (NCE) acrivastine (SPC/GB93/019) and one to its combination with pseudoephedrine (SPC/GB93/090: see above). Acrivastine was a new antihistamine and it was common practice to combine antihistamines with pseudoephedrine. The combination of acrivastine with pseudoephedrine was prima facie obvious once the structure of acrivastine was published and, therefore, one would generally include potential combinations in the patent application on the NCE. An alternative would have been to file a second patent application on possible combinations before the application on the NCE was published but this was not commonly done as the combination was normally considered to be part of the same invention and it was more cost efficient to file the various aspects of the invention in the one application. We note from Dr Rollins's research that other companies adopted a similar practice. For example, Merck & Co's SPC/GB93/002 and SPC/GB93/003 relate to lisinopril and the combination of lisinopril with hydrochlorothiazide (HCTZ) respectively. They are both based on the same basic patent.

A review of chemical combination SPCs on the UKIPO's register from 1994–2011

Looking at the chemical combination SPCs granted between 1994 and 2011 provides a valuable insight into the different approaches taken by pharmaceutical companies when considering what disclosure is required in the basic patent to support the grant of a chemical combination SPC.

There were over 30 chemical combination SPCs granted within this 17-year period. Around 25 per cent of these were based on basic patents which appear to relate to an NCE, with claims also being included in general terms to combinations. When the basic patent relates to an NCE, the second active ingredient is often specified in terms of its activity, e.g. a diuretic, rather than as a specific active. SPCs GB/98/031 (losartan plus HCTZ) and GB/11/010[5] (telmisartan plus HCTZ) both relate to combinations that, like SPC/GB/93/003, contain HCTZ as the second component (i.e. an NCE plus HCTZ). In the case of SPC/GB/11/010 the SPCs on telmisartan, and telmisartan plus HCTZ, were based on the same patent. Conversely, SPC/GB/98/031 is based on a patent filed on a divisional application from the patent on which the "mono" SPC on for losartan alone is based.

Over 50 per cent of the other basic patents reviewed (i.e. other than those on NCEs) that related to chemical combination SPCs contained a claim to the marketed combination where both active ingredients were specifically disclosed in the claims. In the majority of those cases, the patents claimed compositions and/or their uses, with one active being specifically named and the other either being specifically named or listed as one of a number of possible alternatives in the claims. There were only two relevant SPCs,[6] other than those for NCEs, that were based on basic patents which referred to the second active in terms of its activity, e.g. a Reverse Transcriptase Inhibitor in one case or a gestogen in the other.

What is clear from the above is that companies have relied on varying disclosures in the underlying basic patents to justify SPCs over chemical combination products. Some are patents to NCEs with general claims to the combination; some specifically claim the marketed combination or compositions including the combination; some claim one active ingredient in combination with one of a number of possible alternatives; whereas others claim an active ingredient in combination with another active ingredient defined solely in terms of its activity.

A question that therefore arises in light of the recent developments in SPC case law is how the "core inventive advance" test put forward by Arnold J in *Actavis v Sanofi*[7] (and more recently in *Teva v Gilead*[8] and *Teva v Merck*[9]) will impact on the validity of these different types of combination SPCs. Our review of the case law in this article suggests that, in general, such a test would make SPCs on chemical combinations (other than those to specific inventive compositions or uses) almost impossible to obtain. A question to be considered is therefore whether the adoption of such a test is justifiable. Before turning to that question however, we should consider how we got to where we are today.

Where did it all start?

A review of the SPC case law on combination products shows that two key issues frequently arise: (1) what degree of specificity is required in the patent claims for the second component of the combination (the first normally being named specifically—see above), and (2) how many SPCs can be based on one product. Issue (1) relates to art.3(a) and when a combination will be "protected by" the basic patent, and issue (2) relates primarily to art.3(c) and the requirement that the "product has not already been the subject of a certificate". These two issues are often discussed in the same cases and consideration of art.3(a) and art.3(c) have often been merged by the courts, meaning that a decision relating to one these articles generally impacts on the court's approach to interpreting the other.[10]

From a UK perspective, the current state of the law can be tracked back to the decision of Jacob J (as he then was) in *Takeda Chemical Industries Ltd v Comptroller*

[5] This SPC was litigated and the case was subject to a referral to the CJEU in *Actavis Group PTC EHF v Sanofi* (C-443/12) EU:C:2013:833; [2014] R.P.C. 20, which is referred to later in this article.
[6] SPC/GB04/023 and SPC/GB/09/026.
[7] *Actavis Group PTC EHF v Sanofi* [2012] EWHC 2545 (Pat); [2013] R.P.C. 24 at [76].
[8] *Teva UK Ltd v Gilead Sciences Inc* [2017] EWHC 13 (Pat).
[9] *Teva UK Ltd v Merck Sharp & Dohme Corp* [2017] EWHC 539 (Pat); (2017) 155 B.M.L.R. 150.
[10] Arnold J notes the relationship between art.3(a) and art.3(c) as follows in *Teva v Merck* [2017] EWHC 539 (Pat); (2017) 155 B.M.L.R. 150 at [16]: "As is now widely recognised, the interpretation of Article 3(a) and the interpretation of Article 3(c) are both interdependent and dependent on the interpretation of Article 1(b)."

General of the Patent Office.[11] The case concerned the active ingredient lansoprazole in combination with an antibiotic. In an oft-cited passage, Jacob J rejected the adoption of an infringement test for art.3(a) of the SPC Regulation and found that the SPCs at issue failed to satisfy the requirements of that article:

> "7. Mr Alexander, for Takeda, submits that the combination of lansoprazole with an antibiotic, if sold, would infringe the patent … So, the combination is protected by a basic patent which is in force. So, Takeda comply with condition 3(a). Moreover, he submits, definition (b) specifically contemplates that 'product' may be a combination of active ingredients. So it is clear that condition 3(a) contemplates protection of a combination.
>
> …
>
> 10. Mr Birss, for the Comptroller, submits Mr Alexander's argument is flawed. I agree. The so-called 'combination' of lansoprazole and an antibiotic would only infringe because of the presence of the lansoprazole. In truth, the combination is not as such 'protected by a basic patent in force'. What is protected is only the lansoprazole element of that combination. It is sleight-of-hand to say that the combination is protected by the patent. The sleight-of-hand is exposed when one realises that any patent in Mr Alexander's sense protects the product of the patent with anything else in the world. But the patent is not of course for any such 'combination'.
>
> …
>
> 12. … The SPC system is to provide supplementary protection to that provided by the patent—to extend the relevant part of the patent monopoly. It is not a system for providing protection for different monopolies. Here, Takeda's monopoly is in lansoprazole. The monopoly which they seek is a combination of lansoprazole and an antibiotic. The fact that that combination might infringe the monopoly given by the patent simply because one component infringes is irrelevant. Accordingly, I uphold Mr Walker's decision in relation to Art.3(a)."

One can see in Jacob J's comments at [12] the foundation of the "core inventive advance" test currently propounded by Arnold J: i.e. that the focus for art.3(a) purposes should be on determining the core inventive advance of the patent (which in *Takeda* was lansoprazole). If the combination itself does not represent that core inventive advance, then the combination is not "protected by" the patent in the sense required to satisfy art.3(a)—the rationale for this being that patentees should not be able to use SPCs to extend their monopolies for anything other than what embodies the core inventive advance of the basic patent.[12]

However, it is important to note that neither of the basic patents on which the combination SPC applications were based in *Takeda* contained claims to a combination product including an antibiotic. Therefore, it is perhaps unsurprising that Jacob J found as he did, and this explains his view that "any patent in Mr Alexander's sense protects the product of the patent with anything else in the world". Following *Takeda* the CJEU made a number of very important decisions (in the *Medeva*[13] case and its progeny[14]) on what degree of specificity is required in the basic patent for a product to be protected by the basic patent. In short, the CJEU held in those cases that art.3(a) would be satisfied provided that the combination of active ingredients in the medicinal product was "specified/identified"[15] in the wording of the claims. This was the test that was generally applied to art.3(a) until some later CJEU cases dealing with combination products appeared to move towards a core inventive advance test for the purposes of both art.3(a) and art.3(c).

The "core inventive advance" test

In considering the core inventive advance test, it is important to review how the law developed and the rationale behind the proposed adoption of this test. The first mention of the core inventive advance test was by Arnold J in *Actavis v Sanofi*,[16] a case that related to a chemical combination SPC (that of irbesartan and hydrochlorothiazide). In that case Arnold J referred a question on the interpretation of art.3(a) to the CJEU, asking that court (not for the last time—see *Teva v Gilead* below) the following question: "what are the criteria for deciding whether 'the product is protected by a basic patent in force' in Article 3(a) of the [SPC] Regulation?". In providing his own suggested response to this question, he referenced the rejection of the infringement test in *Takeda* and then stated that something more than infringement alone must be required:

[11] *Takeda Chemical Industries Ltd v Comptroller General of the Patent Office* [2003] EWHC 649 (Pat); [2004] R.P.C. 3.
[12] As regards art.3(c), the argument goes that if a patentee has obtained a "mono" SPC for a single active ingredient that embodies the core inventive advance of the basic patent (e.g. lansoprazole), then the patentee should not be permitted to obtain a second SPC over that active ingredient in combination with another active (e.g. an antibiotic) unless that combination is inventive in and of itself. Granting an SPC in such circumstances would be in breach of art.3(c) since the active which represents the core inventive advance of the patent has already been the subject of a certificate.
[13] *Medeva v Comptroller General of Patents, Designs and Trade Marks* (C-322/10) EU:C:2011:773; [2012] R.P.C. 25.
[14] e.g. *University of Queensland, CSL Ltd v Comptroller General of Patents, Designs and Trade Marks* (C-630/10) EU:C:2011:780; *Daiichi Sankyo Co. Ltd and Sanofi-Aventis Deutschland GmbH v DEMO Anonimos Viomikhaniki kai Emporiki Etairia Farmakon* (C-414/11) EU:C:2013:520.16; [2014] Bus. L.R. 1.
[15] In *Medeva* the CJEU used the term "specified". However, in the *University of Queensland* and *Daiichi Sankyo* cases, the Court adopted the same wording for the art.3(a) test but simply switched the word "specified" for "identified". It is generally accepted that nothing turns on this distinction.
[16] *Actavis Group PTC EHF v Sanofi* [2012] EWHC 2545 (Pat); [2013] R.P.C. 24.

> "76 What more is required? In my view, the answer is that the product must infringe because it contains an active ingredient, or a combination of active ingredients, which embodies the inventive advance (or technical contribution) of the basic patent. Where the product is a combination of active ingredients, the combination, as distinct from one of them, must embody the inventive advance of the basic patent."

In its decision on the referral,[17] the CJEU appeared to adopt Arnold J's reasoning and stated as follows at [41]:

> "It should be recalled that the basic objective of Regulation No 469/2009 is to compensate for the delay to the marketing of what constitutes *the core inventive advance* that is the subject of the basic patent, namely, in the main proceedings, irbesartan."(Emphasis added.)

However, the CJEU declined to answer the question put to them by Arnold J on the criteria to be applied when considering art.3(a). This was not, however, the final time that the CJEU would be asked to grapple with this art.3(a) question. In fact, far from it.

Indeed, in the *Lilly v HGS*[18] decision handed down on the same day as *Actavis v Sanofi*, the CJEU offered some further guidance on the level of specificity required for active ingredients in the basic patent to satisfy art.3(a) of the SPC Regulation. The court suggested that art.3(a) would be satisfied where "the claims relate, implicitly but necessarily and specifically, to the active ingredient in question". What this means is open to question (see more on this below). However, what is clear is that there was no mention of a core inventive advance test by the CJEU in this case, which is perhaps unsurprising given that this case did not involve a combination product. Rather, this case involved the question of whether tabalumab (Lilly's antibody product) could be "protected by" a claim which defined a class of antibodies purely by their function (in this case their ability to bind to a novel member of the TNF ligand superfamily of cytokines called Neutrokine-alpha). However, the fact that the CJEU was willing to accept that an antibody claimed generically as part of a wider class of antibodies could (in principle) be "protected" by the relevant basic patent for art.3(a) purposes nicely highlights one of the difficulties with this line of jurisprudence from the CJEU. The tests offered by the CJEU for art.3(a) and art.3(c) come from both single and combination active ingredient cases. However, the CJEU has not sought to distinguish between these types of case, appearing instead to prefer a "one size fits all" policy to the test to be applied for art.3(a) purposes, the result of this being that certain decisions of the court appear inconsistent with one another.

Indeed, in the later case of *Actavis v Boehringer*[19] the CJEU again offered guidance on the level of specificity required for active ingredients in the basic patent to satisfy art.3(a) of the SPC Regulation. Boehringer had already obtained a "mono" SPC for telmisartan alone and were applying for a combination SPC for the combination of telmisartan plus HCTZ. The basic patent contained two claims which covered telmisartan and one of its salts respectively. During the course of the application for the SPC, Boehringer applied to amend the patent at the request of the UKIPO to insert a new claim to the combination of telmisartan and HCTZ. Actavis contended that the SPC was invalid for, inter alia, failure to satisfy art.3(a) as well as on grounds relating to the amendment of the patent. In favouring Actavis's position, the CJEU held at [25] that:

> "Article 3(a) and (c) [of the SPC Regulation] … must be interpreted as meaning 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 holder of that patent has already obtained a supplementary protection certificate, as well as a subsequent claim to a product comprising a combination of that active ingredient and another substance, that provision precludes the holder from obtaining a second supplementary protection certificate for that combination."(Emphasis added.)

Again therefore, the core inventive advance test does not appear in this judgment. The "sole subject matter" test certainly looks similar but the wording used by the CJEU is unhelpful and appears to contradict the earlier decision in *Lilly v HGS*. If the *active ingredient* must constitute the sole subject-matter of the invention, how can it be that a single antibody (such as tabalumab) falling within a much broader class of claimed antibodies satisfies this test? Indeed, t is at the very least arguable that tabalumab (which is the specific active ingredient that obtained a marketing authorisation and thus justified the grant of an SPC) cannot properly be described as the sole subject matter of the invention. Yet the CJEU was clear in *Llily v HGS* that, in principle, tabalumab could be protected by a claim defined solely in functional terms. So where does this leave the current state of the law in the UK?

The current position in the UK

The residual uncertainty left by the CJEU cases discussed above has resulted in a difference of opinion between two judges in the UK as to the correct test to be applied when considering art.3(a) (and art.3(c)) of the SPC Regulation. We have already mentioned the view put forward by Arnold J in *Actavis v Sanofi*, which he subsequently built on in the recent *Teva v Gilead* and *Teva v Merck* cases. However, when the *Lilly v HGS* case returned to the UK

[17] *Actavis Group PTC EHF v Sanofi* (C-443/12) EU:C:2013:833; [2014] R.P.C. 20.
[18] *Eli Lilly v Human Genome Sciences Inc (HGS)* (C-493/12) EU:C:2013:835; [2014] R.P.C. 21.
[19] *Actavis Group PTC EHF v Boehringer Ingelbeim Pharma GmbH & Co KG* (C-577/13) EU:C:2015:165.

High Court following the CJEU's decision, Warren J was also tasked with trying to establish what test should be applied when considering art. 3(a). His decision was handed down before the CJEU's decision in *Actavis v Boehringer* and he suggests a very different test to the core inventive advance test proposed by Arnold J. The following paragraph of Arnold J's judgment in *Teva v Gilead* at [83] neatly summarises the divergence in view:

> "When the [*Lilly v HGS*] case returned to the national court, Warren J struggled at some length to make sense of the guidance given by the [CJEU] ([2014] EWHC 2404 (Pat), [2015] RPC 8) which, like me, he regarded as unclear: see [4] and [63]. I note, however, that he did not refer to the judgment of the Court in *Actavis v Sanofi*. Notwithstanding what the Court had said in *Lilly* at [43], Warren J dismissed Lilly's claim for a declaration. His primary reason for doing so was that he held that claim 13 did 'relate, implicitly but necessarily and specifically' to LY2127399 (now known as tabalumab). If I have understood his reasoning correctly, which I am not sure that I have, he did so because he interpreted the test laid down by the Court as requiring the application of no more than the Extent of Protection Rules (see in particular [40], [43], [54], [58], [65], [70], [73] and [76]), save that he considered that it was not sufficient for a combination product to fall within the scope of a claim due to the presence in the claim of open-ended words such as 'comprising' (see [66]). If that was his reasoning, I regret to say that I respectfully disagree with it. If the Court had meant to say that Article 3(a) simply required the application of the Extent of Protection Rules, it could have stopped the judgment after the words 'as required by Article 69 of the EPC and the Protocol on the interpretation of that provision' in [39]. The Court did not stop there, however. Moreover, Warren J's own qualification recognises that more is required at least in cases involving claims containing words like 'comprising' and combination products. But why should such cases be treated differently? This is not to say that Warren J's conclusion on this issue was wrong, however."

The key section of Warren J's judgment in *Lilly v HGS* case (which is referred to by Arnold J above) states as follows:

> "65. … *If the product falls within the claims, it will be protected within Article 3(a)*. This, however, has to be made subject to one proviso to which I turn.
>
> 66. The proviso relates to products which are combinations of active ingredients and is necessary to reflect the *Medeva* approach where the claims contain some general word or words extending their extent beyond the principal scope of the claims, typically by the use of a word such as 'comprises'. In the absence of such an extending word, the claims have a focused scope and the question is simply whether the product falls within the scope of the claims. In the language of *Medeva*, the question is whether the product (i.e. the combination of active ingredients) is 'specified' in the claims, a question which is answered by a close examination of the claims. If general words are included, the position is different. The product does not fall within the focus of the claims and is not within its scope apart from the general words. In such a case, the product is not 'specified' any more than it is 'specified' where the general words are absent."(Emphasis added.)

In light of this difference of opinion, Arnold J once more referred the following question to the CJEU in *Teva v Gilead*: "What are the criteria for deciding whether 'the product is protected by a basic patent in force' in Article 3(a) of the SPC Regulation?". Copying verbatim from his statements at [76] of *Actavis v Sanofi* (see above), Arnold J reiterated his view that something more is required than that the product falls within the scope of protection of the claims[20]:

> "97. What more is required? In my view, the answer is that the product must infringe because it contains an active ingredient, or a combination of active ingredients, which embodies the inventive advance (or technical contribution) of the basic patent. Where the product is a combination of active ingredients, the combination, as distinct from one of them, must embody the inventive advance of the basic patent … A medicinal product whose active ingredients are [tenofovir disoproxil] and another therapeutic agent such as emtricitabine in combination is not protected by the Patent within the meaning of Article 3(a) because the combination, as distinct from [tenofovir disoproxil], does not embody the inventive advance of the Patent. This is not a question of the wording

[20] Arnold J refers to falling within the scope of the claim as the "Extent of Protection Rules"—see *Teva v Gilead* [2017] EWHC 13 (Pat) at [83], cited above.

> of the claims of the basic patent, which as discussed above can be manipulated by the patent attorney who drafts it, but of its substance."

So it is evident that, on the one hand, Arnold J is propounding a "core inventive advance" test where the substance of the patent's disclosure, rather than the wording of the claims, takes precedence. In summary, if the combination is not itself inventive (i.e. inventive over and above the inventiveness of any specific active ingredient also claimed therein), SPC protection should not be available for it. On the other hand, Warren J is suggesting that art.3(a) should be satisfied where the product "falls within the claims", except in the case of combination products where a combination only falls within the claims by virtue of some extending wording such as "comprises". For Warren J, it is the wording of the claims that takes precedence.

It is submitted that Warren J's test is to be preferred. His proviso suggests that the combination must in fact be specified/identified in the claims rather than solely falling within the claims because the combination infringes a claim to only one of the active ingredients. This approach is very similar to the *Medeva* test for combinations, except that Warren J's approach to the patent claim at issue in *Lilly v HGS* suggests that generically claiming the second active ingredient in the combination should also be sufficient to satisfy the *Medeva* test (an approach that we would also endorse but which is not clear based on *Medeva* alone). It is interesting to note at this point Arnold J's recent decision in *Sandoz v Searle*,[21] where he held that a single chemical active ingredient could be "protected by" a Markush claim for art.3(a) purposes. In light of this decision, it is unclear why generically claiming the second active ingredient in a combination should not also suffice for art.3(a) purposes, though Arnold J did make a point of finding that darunavir (the relevant active ingredient in that case) embodies the inventive advance of the underlying patent.[22]

If one assumes that Warren J has taken the correct approach, we would suggest that art.3(c) should not be used as a way to invalidate combination SPCs effectively by the back door. Article 1(b) of the SPC Regulation states that "product" means the active ingredient or *combination of* active ingredients of a medicinal product. So the question should be whether the combination of active ingredients has already been the subject of a certificate. There is nothing in the wording of the SPC Regulation to suggest that, when looking at a combination product, one should in fact focus on whether one active within the combination embodies the core inventive advance of the underlying patent and has already been the subject of an SPC. Indeed, imparting such a test into art.3 reads significant additional requirements into the wording of the SPC Regulation and significantly limits the availability of SPCs for combination products.

Combination product SPCs in practice

If it is considered that the purpose of an SPC is to provide SPC holders with effective periods of patent protection in order to cover the R & D investment put into developing medicinal products (and thereby encourage the development of further products), it would appear that the key integer should be whether a marketing authorisation for a product protected by a patent has been granted and not that the product represents the core inventive advance of the underlying patent. It should not be forgotten that obtaining a marketing authorisation for a combination product requires the investment of considerable time and effort, which may not be as great as that required to obtain a marketing authorisation on an NCE, but is still significant. Indeed, it would appear from the data above that for chemical combination SPCs filed between 2009 to 2011 (with the exception of two SPCs) far more than half the patent term had expired before a marketing authorisation was obtained, hence why the average time from marketing authorisation to SPC expiry was 10.6 years (which is far less than the 15 years envisaged by Recital 9 of the SPC Regulation).

The UK Court and the CJEU in fact recognised in the *Daiichi* case[23] "that Daiichi Sankyo invested considerable time and resources in undertaking clinical trials and studies in order to secure a MA in respect of such a combination therapy". As such, it is not entirely clear why the validity of SPCs for combination products should be put at far greater risk by the adoption of a core inventive advance test. It is true that the patentee will, in many cases, have already obtained a "mono" SPC covering one of the active ingredients in the combination alone. However, this is not always so,[24] and does not change the fact that a separate marketing authorisation (which involves significant time, resources and expense for the patentee) is required for combination products. Further, the core inventive advance approach seems to ignore the potential patient benefits which are provided by combination products. If innovators are unable to recuperate the costs involved in bringing combination products to market, then what incentive do they have to continue to develop these products in the future? This is a question which does not seem to have been expressly addressed in any of the cases discussed in this article. Rather, the CJEU has simply stated that allowing SPC protection for combination products in the cases before it would have been

[21] *Sandoz Ltd v GD Searle LLC* [2017] EWHC 987 (Pat).
[22] *Sandoz Ltd v GD Searle LLC* [2017] EWHC 987 (Pat) at [67].
[23] *Daiichi Sankyo Co. Ltd and Sanofi-Aventis Deutschland GmbH v DEMO Anonimos Viomikhaniki kai Emporiki Etairia Farmakon* (C-414/11) EU:C:2013:520.16; [2014] Bus. L.R. 1
[24] See, e.g., *Teva v Gilead* [2017] EWHC 13 (Pat) at [24].

> "contrary to the requirement to balance the interests of the pharmaceutical industry and those of public health as regards the encouragement of research within the European Union by the use of SPCs".[25]

What is particularly interesting about this justification is that it appears to be drawn primarily from Recital 10 of the SPC Regulation, which expressly links the balance of interests between industry and the public health to (1) the limitation of SPC protection to a maximum of five years, and (2) the limitation of SPC protection to the product which obtained a marketing authorisation. At no point does the SPC Regulation suggest that SPCs should be less available for combination products than any other type of product.

Further, the judgments discussed herein do not cite any research or provide any statistics in relation to the costs involved in bringing chemical combination products to market and the potential impact that the courts' decisions might have on innovation following the limitation of SPC protection for chemical combination products. As mentioned above, the SPC Regulation clearly states that applicants can obtain SPCs for combination products, and there is nothing in the wording of the Regulation which suggests that such protection should only extend to combinations which are inventive per se. That is a significant addition to the wording of the SPC Regulation and one which is at odds with the "simple and transparent" system which (as Arnold J himself accepts[26]) was the intention for the SPC system when it first came into effect.

Potential problems with the core inventive advance approach

As mentioned above, we do not favour the adoption of a core inventive advance test. The key aspect of this test is that the patentee must show not only that the combination of active ingredients falls within the wording of the claims but also that the combination embodies the inventive advance of the basic patent. So, what this test requires is an assessment of the independent validity of the claimed combination. Surely then, such an analysis must involve at least (1) interpretation of the claims; (2) consideration of any relevant prior art; and (3) assessment of any invalidity arguments and counter-arguments raised by the SPC holder regarding novelty and obviousness in relation to each relevant piece of prior art. It may be that in some cases this analysis is straightforward, requiring little judicial time and scrutiny. However, some cases will clearly be far more complex (e.g. where it is not clear whether the combination was obvious at the priority date or not) and so in practice such a test will inevitably result in additional expert evidence and, in the UK, cross-examination. Further, anyone attacking the validity of an SPC will presumably have to provide detailed pleadings setting out for each piece of prior art their novelty and obviousness cases, in much the same way as one has to do when attacking the validity of a patent.

An additional important point in this regard is that the core inventive advance test also appears to require the combination to be novel and inventive not only over the prior art but also over other disclosures in the patent, e.g. the disclosure of one of the active ingredients in the combination which is also claimed alone. Indeed, Arnold J suggested in *Teva v Merck* at [170] that the question to be asked when applying the core inventive advance test is in fact not the "conventional" patent law question:

> "The question to be considered is not the conventional one of whether a claim is invalid over a particular item of prior art read in the light of the common general knowledge, but whether, *given the invention of efavirenz*, claim 16[27] represents a distinct invention such that it could in principle form the subject-matter of a separate patent."(Emphasis added.)

So the claimed combination must represent a distinct invention over and above one of the other active ingredients disclosed in that patent, when that active ingredient was new and inventive to the skilled person reading the patent at the priority date. This imposes a much higher hurdle on the requirements for obtaining an SPC for a chemical combination product when compared to obtaining SPCs for single active products. Again, given the lack of data and information which appears to have been considered by the courts when deciding to restrict the availability of SPCs for combination products, it is unclear whether the policy considerations put forward really do justify the adoption of such a high threshold test. At the very least, the adoption of a core inventive advance test will likely move us much further from the "simple and transparent system" envisaged when the SPC system came into being.

In this regard, one policy argument that is often relied on in favour of restricting the availability of combination SPCs and is worth considering further is the argument first touched upon in *Takeda*, and subsequently built on by the CJEU, that permitting SPC protection for an active ingredient "in conjunction with an unlimited number of other active ingredients which do not constitute the subject-matter of the invention"[28] would be contrary to the balance of interests between industry and the public health. In our view, this argument can only go so far. The test from *Medeva* requires the combination to be "specified/identified" in the wording of the claims. Warren J adopted this test subject to the proviso that it will not be enough that the combination only falls within the claim due to the use of "extending" words. So, the

[25] *Actavis Group PTC EHF v Boehringer* (C-577/13) EU:C:2015:165 at [36]; and *Actavis Group PTC EHF v Sanofi* (C-443/12) EU:C:2013:833, [2014] R.P.C. 20 at [41].
[26] *Sandoz Ltd v GD Searle LLC* [2017] EWHC 987 (Pat) at [67].
[27] Claim 16 states as follows: "A combination of the compound of claim 12 or a pharmaceutically acceptable salt thereof with a nucleoside analog having biological activity against HIV reverse transcriptase."
[28] *Actavis Group PTC EHF v Boehringer* (C-577/13) EU:C:2015:165 at [36].

combination must be set out in the claims in order to satisfy art.3(a). This requirement brings with it its own consequences for the patentee. In particular, the claimed combination must be sufficient. Therefore, it is not the case that the patentee would be able to claim an active ingredient in conjunction with "an unlimited number of other active ingredients". If the patentee were to include overly broad claims to one active ingredient in combination with any other active ingredient in the world, those claims would be susceptible to an invalidity attack for, e.g., lack of plausibility and not being enabled across their breadth. Further, one must not forget the requirements in art.3(b) that the combination product must be the subject of an MA. As mentioned above, if an SPC applicant has had to invest significant R & D expenditure in bringing a new combination product to market, why should they not be able to obtain an SPC covering that product, particularly where it offers patient benefits over and above alternative single active ingredient products (to the extent that such a mono active ingredient product even exists on the market)?

In short, introducing a new criterion, that the combination should be novel and inventive in and of itself, would be to introduce a new standard that is neither implicit or explicit in the wording of the SPC Regulation. Furthermore, it would make SPCs on chemical combinations, other than those to specific inventive compositions or uses, almost impossible to obtain. Consider the case of an invention of a new sartan. It is likely at some point to be combined with a diuretic, particularly HCTZ, but such a combination is likely to be prima facie obvious unless the combination has a surprisingly advantageous property. Similarly, a new anti-retroviral compound is likely to be combined with other anti-viral compounds for the treatment of HIV infections, or a new anti-diabetic may well be combined with metformin. However, when the patent on the new compound is filed, the specific combinations, and there may be more than one, that are eventually marketed are unlikely to have been finally chosen. The second component of the combination could well be selected from those available at the time the patent filing was made, however, and such a selection may well not involve an inventive step so that no SPC is possible under the proposal made by Arnold J. Is it right that the developer of these combinations is not entitled to combination SPC protection? For the reasons set out in this article, we would submit that it is not.

Proposed approach

Our view is that the approach taken by Warren J in *Lilly v HGS* is to be preferred for SPCs on combination products. In essence, it is equivalent to the test in *Medeva*, i.e. that provided the combination is claimed in the patent, that should be sufficient to satisfy art.3(a) and art.(c) of the SPC Regulation. However, Warren J's approach to claim 16 in that case goes slightly further by suggesting that claiming an active ingredient within a class should be sufficient for art.3(a) purposes. Thus, our view is that generically claiming the second active ingredient in a combination (e.g. by its activity) should also be sufficient.

As regards art.3(c), "product" as defined in art.1(b) includes combinations of active ingredients. Therefore the question should be whether the *combination* has previously been the subject of an SPC and not whether one of the active ingredients, which is alleged to embody the core inventive advance of the basic patent, has previously been the subject of an SPC.

The approach taken by the courts should be simple: (1) the claims should be construed as at the priority date of the basic patent; and then, once the construction of the claims has been decided, (2) the question of whether the marketed combination falls within the claims of the basic patent should be determined once that marketed combination is known. If Warren J's approach to art.3 were to be adopted, answering the second question would be straightforward, given the requirement (taken from *Medeva*) that the combination be specifically claimed in the basic patent. Such an approach to art.3(a) and art.3(c) would be consistent with the "simple and transparent" approach to the SPC system that was intended by the EU legislator when the SPC Regulation first came into effect.