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Supplementary Protection Certificates

May a part of a fusion protein be considered an *"active ingredient"*? Yes, says the ECJ in Forsgren

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1 Background

Supplementary protection certificates (SPCs) compensate for the delay in commercializing patented medicinal or plant protection products, which is caused by marketing authorization (MA) procedures that are a prerequisite for placing the respective product on the market. In many cases, the extended protection conferred by SPCs is a necessary instrument for applicants to render the development of new plant protection and medicinal products profitable at all. They may therefore be regarded as pivotal incentives for innovation in their respective fields.

In order to obtain an SPC, it is necessary, *inter alia*, that the product is protected by a basic patent and is subject of a MA. These requirements are set out in Article 3 (a) and 3 (b) of EC Regulation (ECR) 469/2009, respectively.

In the recent years, a controversial debate emerged about how Article 3 (a) should be interpreted with regard to combination products.

In decision C-518/10 *(Yeda),* the European Court of Justice (ECJ) stated that an SPC may not be obtained for a single active ingredient, if it *"is not the subject of any claim relating to that active ingredient alone"*, i.e. when the claims only disclosed the active ingredient in combination with another active ingredient.

However, an SPC may be obtained for a single active ingredient if both the basic patent and the MA are directed to combination products, as long as the basic patent also protects the single ingredient as such. An additional SPC for the single ingredient may even be obtained if another SPC for the combination product has already been granted based on the same patent (decision C-484/12; *Georgetown II*).

In a similar constellation, it is also possible to obtain an SPC for a single active ingredient if the basic patent protects only this single active ingredient, and the MA relied on for the SPC application is directed to a combination product comprising this active ingredient (decision C-630/10; *Queensland* and decision C-422/10; *Georgetown I*).

Another controversial question was the interpretation of the criteria, which have to be met to be considered as *"products"* and *"active ingredients"* according to EC Regulation 469/2009.

Article 1 (a) of ECR 469/2009 defines a *"medicinal product"* as

"[...] any substance or combination of substances presented for ***treating or preventing disease*** *in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to* ***restoring, correcting or modifying physiological functions*** *in humans or in animals"* (emphasis added).

Article 1 (b) of ECR 469/2009 further states that

"'product' means the active ingredient or combination of active ingredients of a medicinal product".

In decision C-11/13 *(Bayer Crop Science)*, the ECJ decided that an

"active substance", according to ECR 1610/96, *"may cover a substance intended to be used as a safener, where that substance has a toxic, phytotoxic or plant protection action of its own".*

However, in decision C-210/13 *(GSK)*, it was ruled that

"[...] an ***adjuvant does not fall within the definition of 'active ingredient'*** *within the meaning of that provision, so a combination of two substances, namely an*

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active ingredient having therapeutic effects on its own, and an ***adjuvant which, while enhancing those therapeutic effects, has no therapeutic effect on its own, does not fall within the definition of 'combination of active ingredients'*** *[...]"* (emphasis added).

According to Article 4 of ECR 469/2009, the scope of protection of the SPC is limited to the product and its application, which are covered by the MA:

"Within the limits of the protection conferred by the basic patent, the protection conferred by a certificate shall extend ***only to the product covered by the authorization*** *to place the corresponding medicinal product on the market and for any* ***use of the product*** *as a medicinal product* ***that has been authorised*** *before the expiry of the certificate"* (emphasis added).

As discussed in more detail herein below, this provision is not only relevant in the context of further medical use (i.e. new indications), but also with respect to medicinal products which are suitable for the prevention or treatment of multiple indications, in particular vaccine combinations.

2 The Forsgren case

Mr. Forsgren is the proprietor of European patent EP 0 594 610, titled *"Protein D – an IgD-binding protein of Haemophilus influenza"*. Protein D is a viral surface lipoprotein, which was the first non-typeable *H. influenzae* antigen to induce a protective immune response in humans.

Glaxosmithkline (GSK) has obtained a MA for *"Synflorix"* (EC decision C(2009)2563), titled *"Pneumococcal polysaccharide conjugate vaccine (adsorbed)"*, whose therapeutic indications according to the MA are *"[a]ctive immunisation against invasive disease, pneumonia and acute otitis media [middle ear inflammation] caused by Streptococcus pneumoniae in infants and children from 6 weeks up to 2 years of age"*. Synflorix contains several pneumococcal polysaccharides, which are conjugated to different carrier proteins, one of which is protein D. Despite its potential action as an influenza antigen, the MA of Synflorix only described it as a carrier protein, and noted that its action as a vaccine against *H. influenzae* (which may also cause middle ear inflammation) was not proven.

Based on EP 0 594 610 as the basic patent and the MA for Synflorix, Forsgren applied for an SPC at the Austrian Patent Office, which was rejected for the reason that protein D was *"just an excipient"*. This statement was reasoned based on the observation that - although protein D actually exhibits an effect against *H. influenzae* - the MA defined Synflorix as a vaccine against pneumococci.

The Remedies Department (Rechtsmittelabteilung) of the Austrian Patent Office confirmed this decision, and stated that protein D is not contained in Synflorix as such, since it is covalently linked to another substance, thus making it a different active ingredient.

Thus, Forsgren lodged an appeal to the Österreichischer Oberster Patent- und Markensenat (Austrian Supreme Patent and Trade Mark Adjudication Tribunal; 'the referring court').

Forsgren argued that protein D has the same therapeutic effect when it is covalently linked to other active ingredients as in the case when it is not covalently linked to another substance. Moreover, in light of the *Medeva* and *Georgetown* decisions, an SPC may be granted for a combination product, even if only one of its active ingredients is protected by a basic patent.

The court stayed the proceedings and made a referral to the ECJ. In its order for reference, the referring court concluded:

– Protein D is protected by a basic patent;

- No SPC has been granted yet for Protein D;
- A MA for Synflorix has been granted;
- In Synflorix, Protein D has an action of its own, namely:
  as a **vaccine against** a middle ear inflammation caused by non-typable ***Haemophilus influenzae*** bacteria; and
  as an **adjuvant** for the substances acting **against pneumococci** (pneumococcal polysaccharides).

According to the referring court, the admissibility of an SPC in this case thus depended on whether Protein D may be regarded as an active ingredient of the medicinal product Synflorix. The court hence referred the following questions to the ECJ:

*'**1.** Under Article 1(b) and Article 3(a) and (b) of [Regulation No 469/2009], provided that the other conditions are met, may [an SPC] be granted for an active ingredient protected by a basic patent (in this case, Protein D) where that active ingredient is present in a medicinal product (in this case, Synflorix) **as part of a covalent (molecular) bond with other active ingredients but none the less retains an effect of its own**?*

2. *If Question 1 is answered in the affirmative:*
(a) *Under Article 3(a) and (b) of [Regulation No 469/2009], may [an SPC] be granted for the substance protected by the basic patent (in this case, Protein D) where that **substance has a therapeutic effect of its own** (in this case, as a vaccine against the Haemophilus influenzae bacterium) but the **marketing authorization for the medicinal product does not relate to that effect**?*
(b) *Under Article 3(a) and (b) of [ECR 469/2009], may [an SPC] be granted for the substance protected by the basic patent (in this case, Protein D) where the marketing authorization describes that substance as a 'carrier' for the actual active ingredients (in this case, pneumococcal polysaccharides), where the substance, as an **adjuvant**, enhances the effect of those substances, but where that **effect is not expressly mentioned in the marketing authorization** for the medicinal product?'* (emphasis added)

The case was handled at the ECJ under No. C-631/13, *Forsgren*.

3 The ECJ's decision

Question 1 was reformulated by the ECJ as whether Articles 1(b) and 3(a) must be interpreted as precluding the possibility that an active ingredient can give rise to the grant of an SPC on the sole ground that the active ingredient is covalently bound to other active ingredients forming part of a medicinal product.

The court noted that according to decision C-431/04 *(Massachusetts Institute of Technology, MIT)*, the expression *"active ingredient"* does not cover substances forming part of a medicinal product which do not have an effect of their own on the human or animal body. This provision has later been adopted (in a similar wording) into Article 1 of directive 2001/83/EC.

The ECJ concluded that the term *"active ingredient"*, for the purposes of applying ECR 469/2009, thus concerns substances producing a pharmacological, immunological or metabolic action of their own. Since ECR 469/2009 does not discriminate according to whether an active ingredient is covalently linked to other substances, the ECJ decided that an SPC may be granted for an active ingredient which produces a pharmacological, immunological or metabolic action of its own, independently of covalent binding with other active ingredients.

Regarding **question 2 a)**, the ECJ interpreted the question as, in essence, relating to whether Article 3(b) of ECR 469/2009 precludes the grant of an SPC for an active ingredient whose therapeutic effect does not fall within the therapeutic indications covered by the wording of the MA. The ECJ accordingly noted that

Article 4 of ECR 469/2009 implies that the **use** of a product, which has **not been authorized by the MA,** may not be covered by an SPC. The court thus came to the conclusion that an active ingredient whose therapeutic effects do not fall within the therapeutic indications for which a MA was granted may not give rise to the grant of an SPC.

The ECJ additionally referred to decisions C-442/11 and C-574/11 (*Novartis* decisions) according to which an SPC for one active ingredient also provides protection for all combination products containing this active ingredient together with another active ingredient if authorized for the same therapeutic indication. Based on the fact that the MA for Synflorix did not provide clinical data about its effect against *H. influenzae*, the ECJ concluded that clinical trials did not delay the economical exploitation of Protein D. Therefore, in the present case, the grant of an SPC would contravene the purpose of ECR 469/2009, namely the compensation for the delay caused by a MA procedure.

It was thus concluded that an active ingredient whose therapeutic effects do not fall within the therapeutic indications of the corresponding MA is not eligible for an SPC.

In view to **question 2 b)**, the ECJ wished to answer the reformulated question whether Article 3(b) of ECR 469/2009 must be interpreted as precluding the grant of an SPC for a product referred to in the MA as the carrier protein of an active ingredient, on the ground that said protein, as an adjuvant, enhances the effect of an active ingredient without that effect being expressly mentioned in the MA. The ECJ observed that Protein D is neither described as an adjuvant nor as an excipient in the MA of Synflorix. It therefore held that decision C-210/13 *(GSK)*, which stated that an adjuvant is not an active ingredient according to ECR 469/2009, is **not applicable** in the present case.

In this respect, the ECJ found that it was essential to clarify whether a carrier protein, which does not have an effect of its own that falls under the indication according to the corresponding MA, does elicit such an effect as soon as it is conjugated to other active ingredients forming part of a medicinal product. by a covalent bond. The ECJ held that this question is neither addressed explicitly in ECR 469/2009, nor can it be readily answered by an analogy to the *Bayer Crop Science* decision (C-11/13; *vide supra*). It was therefore concluded that it must be determined whether Protein D, in its conjugated form to other active ingredients, produces a pharmacological, immunological or metabolic action of its own, and whether that effect actually falls within the therapeutic indications covered by the wording of the MA.

Ultimately, the ECJ answered the referred questions as follows:

*"**1.** Articles 1(b) and 3(a) [of ECR 469/2009] must be interpreted as not precluding, in principle, the possibility that an active ingredient can give rise to the grant [of an SPC] where the active ingredient is covalently bound to other active ingredients which are part of a medicinal product.*

***2.** Article 3(b) [of ECR 469/2009] must be interpreted as precluding the grant of a [SPC] for an active ingredient whose effect does not fall within the therapeutic indications covered by the wording of the [MA].*

Article 1(b) of [ECR 469/2009] must be interpreted as meaning that a carrier protein conjugated with a polysaccharide antigen by means of a covalent binding may be categorized 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 [MA], 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."

4 The decision of the Austrian Supreme Court

After the ECJ's decision, the case was continued before the Austrian Supreme Court (Oberster Gerichtshof, decision 4 Ob 20/15t). Based on the ECJ's answer on the first part of question 2, the court concluded that the effect of protein D as a vaccine against *H. influenza* cannot justify the grant of an SPC, since this effect does not fall within the therapeutic indications covered by the wording of the MA. Accordingly, the court stated that it is relevant to assess, according to the ECJ's answer on the second part of question 2, whether protein D produces a pharmacological, immunological or metabolic action of its own which is covered by the therapeutic indication of the MA, i.e. an action against pneumococci. Most importantly, based on the ECJ's statement that this question should be determined *"in the light of all the facts of the dispute in the main proceedings"*, the court concluded that **it is not relevant alone whether the compound is described as an *"active ingredient"* in the MA, but it is rather sufficient that it actually exhibits such an effect.** Accordingly, the court remitted the case to the previous instance for the taking of evidence in this respect.

5 Conclusion and comments

This ECJ's decision at least provides some clarification as to the question whether the covalent binding of one active ingredient to another active ingredient is of relevance. However, the specific requirements of producing *"a pharmacological, immunological or metabolic action of its own"* have not been fully developed by the Court, since it left this question to the referring court to be answered. At least according to the preliminary ruling of the Austrian Patent Office, this requirement appears to be met by Protein D in the present case.

More importantly, the present decision limits the definition of a product or active ingredient comprised in a product which is governed by Article 3 of ECR 469/2009 and relates to *"conditions for obtaining a certificate"* by additional considerations regarding the subject-matter of protection according to Article 4 ECR 469/2009. In particular, the provision of Article 4 that the use of the product according to the MA may limit the protection conferred by the basic patent is construed as indication for a general purpose-limitation of the notion *"product"*, since according to this interpretation therapeutic indications for a product have also to be taken into account.

It seems questionable whether the conclusion of the ECJ complies with the intention of the legislator. That is, one should ask whether the provision of Article 4 ECR 469/2009 was intended to define substantive prerequisites for obtaining an SPC. The conditions for obtaining an SPC which are provided in Article 3 should not be commingled with the hints of **the subject matter of protection according to Article 4**. Thus, since Article 4 clearly regulates the **effect** of an SPC, it is difficult to follow the ECJ' s logic which uses the definition of the effect to conclude on permissibility questions. It is, in particular, difficult to understand why the ECJ intends to introduce elements of the construction of the scope of protection into the SPC granting procedure since such an approach renders the question of what is actually a medicinal product even more complex, while leaving the definition of the scope of protection essentially unchanged.

Despite this once more enigmatic ruling of the ECJ, SPC applicants have now been provided with the principle option to apply for an SPC which is directed to one component of a combination of covalently linked active ingredients. It would seem reasonable to assume that this ruling may be interpreted in that it does apply analogously for combinations of small molecule drugs, as well as for small molecule / protein constructs which are covalently linked, respectively. It seems that the ECJ considers the functionally distinct parts of such molecules as

individual substances irrespective of the covalent bonds. Taking into consideration the present decision, applicants should ensure that the MA of a product for which an SPC is sought should, already at the time of the SPC application, provide evidence that the relevant active ingredient produces a *"pharmacological, immunological or metabolic action of its own"* which is covered by the therapeutic indications of the MA.

In view of the subsequent decision of the Austrian Supreme Court, it does not appear to be necessary that any potential active ingredient which may be the subject of an SPC is explicitly described as such in the MA, but instead it seems to be sufficient that it **actually inhibits a medical action of its own** according to the provisions of Article 1(a) of ECR 469/2009.

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