Court of Justice EU, 14 November 2013, GSK v Patent Office

PATENT LAW - SPC

Adjuvant does not fall within the definition of 'active ingredient' within the meaning of the provision, and adjuvant which has no therapeutic effect on its own does not fall within the definition of 'combination of active ingredients'

- **In the light of all the foregoing considerations, the answer to the questions referred is that Article 1(b) of Regulation No 469/2009 must be interpreted as meaning that, just as 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 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' within the meaning of that provision.**

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Court of Justice EU, 14 November 2013

(A. Ó Caoimh, acting as President of the Eighth Chamber, C. Toader (Rapporteur) and E. Jarašiūnas)

ORDER OF THE COURT (Eighth Chamber)

14 November 2013 (*)

(Medicinal products for human use – Supplementary protection certificate – Regulation (EC) No 469/2009 – Concepts of 'active ingredient' and 'combination of active ingredients' – Adjuvant)

In Case C‑210/13,

REQUEST for a preliminary ruling under Article 267 TFEU from the High Court of Justice (England and Wales), Chancery Division (Patents Court) (United Kingdom), made by decision of 25 March 2013, received at the Court on 18 April 2013, in the proceedings

Glaxosmithkline Biologicals SA,

Glaxosmithkline Biologicals, Niederlassung der Smithkline Beecham Pharma GmbH & Co. KG,

v

Comptroller-General of Patents, Designs and Trade Marks

THE COURT (Eighth Chamber),

composed of A. Ó Caoimh, acting as President of the Eighth Chamber, C. Toader (Rapporteur) and E. Jarašiūnas, Judges,

Advocate General: N. Jääskinen,

Registrar: A. Calot Escobar,

having decided, after hearing the Advocate General, to give a decision by reasoned order, in accordance with Article 99 of the Rules of Procedure of the Court of Justice,

makes the following

Order

1 This reference for a preliminary ruling concerns the interpretation of Article 1(b) 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 (OJ 2009 L 152, p. 1).

2 The reference has been made in proceedings between Glaxosmithkline Biologicals SA and Glaxosmithkline Biologicals, Niederlassung der Smithkline Beecham Pharma GmbH & Co. KG (together, 'GSK') and the Comptroller General of Patents, Designs and Trade Marks ('the Patent Office') concerning the latter's refusal to grant GSK two supplementary protection certificates ('SPC').

Legal context

3 Recitals 4 to 10 in the preamble to Regulation No 469/2009 read as follows:

'(4) At the moment, the period that elapses between the filing of an application for a patent for a new medicinal product and authorisation to place the medicinal product on the market ['MA'] makes the period of effective protection under the patent insufficient to cover the investment put into the research.

(5) This situation leads to a lack of protection which penalises pharmaceutical research.

(6) There exists a risk of research centres situated in the Member States relocating to countries that offer greater protection.

(7) A uniform solution at Community level should be provided for, thereby preventing the heterogeneous development of national laws leading to further disparities which would be likely to create obstacles to the free movement of medicinal products within the Community and thus directly affect the functioning of the internal market.

(8) Therefore, the provision of an [SPC] granted, under the same conditions, by each of the Member States at the request of the holder of a national or European patent relating to a medicinal product for which [MA] has been granted is necessary. A regulation is therefore the most appropriate legal instrument.

(9) The duration of the protection granted by the certificate should be such as to provide adequate effective protection. For this purpose, the holder of both a patent and a certificate should be able to enjoy an overall maximum of 15 years of exclusivity from the time the medicinal product in question first obtains authorisation to be placed on the market in the Community.

(10) All the interests at stake, including those of public health, in a sector as complex and sensitive as the pharmaceutical sector should nevertheless be taken into account. For this purpose, the certificate cannot be granted for a period exceeding five years. The protection granted should furthermore be strictly confined to the product which obtained authorisation to be placed on the market as a medicinal product.'

4 Article 1 of Regulation No 469/2009, headed *'Definitions', provides as follows:*

'For the purposes of this Regulation, the following definitions shall apply:

(a) "medicinal products" means any substance or combination of substances presented for treating or preventing disease in human beings …;

(b) "product" means the active ingredient or combination of active ingredients of a medicinal product;

(c) "basic patent" means a patent which protects a product as such, a process to obtain a product or an application of a product, and which is designated by its holder for the purpose of the procedure for grant of a certificate;

(d) "certificate" means the [SPC];

…'

5 Article 2 of Regulation No 469/2009 reads as follows:

'Any product protected by a patent in the territory of a Member State and subject, prior to being placed on the market as a medicinal product, to an administrative authorisation procedure as laid down in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [OJ 2001 L 311, p. 67] … may, under the terms and conditions provided for in this Regulation, be the subject of a certificate.'

6 Article 3 of Regulation No 469/2009, entitled *'Conditions for obtaining a certificate', provides as follows:*

'A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:

(a) the product is protected by a basic patent in force;

(b) a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC …;

(c) the product has not already been the subject of a certificate;

(d) the authorisation referred to in point (b) is the first authorisation to place the product on the market as a medicinal product.'

7 Article 4 of Regulation No 469/2009, headed *'Subject matter of protection', states as follows:*

'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 authorisation 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.'

8 Article 5 of Regulation No 469/2009, concerning the '[e]ffects of the certificate', is worded as follows:

'Subject to the provisions of Article 4, the certificate shall confer the same rights as conferred by the basic patent and shall be subject to the same limitations and the same obligations.'

The dispute in the main proceedings and the questions referred for a preliminary ruling

9 On 10 October 2008, GSK filed SPC application SPC/GB08/046 for a product described as an 'oil in water emulsion comprising squalene, DL-α-tocopherol and polysorbate 80', an adjuvant known as AS03, which is protected by European Patent (UK) No 0 868 918.

10 On 18 August 2011, GSK filed another SPC application (SPC/GB11/043) for a product described as *'an adjuvanted influenza vaccine comprising an influenza virus component which is an influenza virus antigen from an influenza virus strain that is associated with a pandemic outbreak or has the potential to be associated with a pandemic outbreak, wherein the adjuvant is an oil in water emulsion comprising squalene, DL-α-tocopherol and polysorbate 80'*. That SPC application therefore related to a vaccine protected by European Patent (UK) No 1 618 889 comprising an antigen and AS03.

11 In support of both those applications, GSK relied on MA EU/1/08/453/001 issued on 14 May 2008 by the European Medicines Agency ('the EMA') for a pre-pandemic influenza vaccine against the H5N1 subtype of influenza A virus marketed by GSK under the trade mark Prepandrix. It is apparent from the order for reference that that vaccine comprises an antigen known as A/Indonesia/05/2005 (H5N1)-like strain used (PR8-IBCDC-RG2) together with AS03. Studies have demonstrated that the presence of AS03 is an important factor in ensuring that the vaccine satisfies the criteria for licensing by the United States Food and Drug Administration and the EMA.

12 By decision of 19 December 2012, the Patent Office decided that neither SPC application was allowable as it stood, on the ground that AS03 was not an 'active ingredient' of Prepandrix. However, it indicated that it was prepared to give GSK the opportunity to amend its applications.

13 The Patent Office considered, in particular, that in the light of the judgment in Case C-431/04 *Massachussets Institute of Technology* [2006] ECR I-4089, since AS03 did not have a therapeutic effect on its own, that adjuvant could not be regarded as an active ingredient within the meaning of Article 1(b) of Regulation No 469/2009, whether in its own right or in combination with the antigen contained in Prepandrix. ASOC did not itself confer any immunity, whether against influenza or any other condition. The fact that AS03 enhanced the therapeutic effect of the antigen, irrespective of the actual antigen involved and the immunological protection sought, was not sufficient to enable it to be regarded in itself as an active ingredient.

14 GSK challenged the Patent Office's decision not to grant SPCs before the referring court.

15 First, GSK relies on various paragraphs of the Explanatory Memorandum to the Proposal for a Council Regulation (EEC) of 11 April 1990, concerning the creation of a supplementary protection certificate for medicinal products (COM(90) 101 final), in particular paragraph 11 thereof. According to GSK, it is clear from those paragraphs that Regulation No 469/2009 was intended to apply to all new products which were the subject of innovative research, save only for minor variants such as a new dose, the use of a different salt or ester or a different pharmaceutical formulation.

16 Second, GSK submits that, in the light of the judgment in Case C‑130/11 *Neurim Pharmaceuticals* (1991) [2012] ECR, Article 1(b) of Regulation No 469/2009 should no longer be narrowly interpreted.

17 Third, GSK claims that the present case can be distinguished from the case which gave rise to the judgment in *Massachussets Technology Institute*. That case was concerned only with an excipient which had no physiological effect on the body, whereas the main proceedings are concerned with an adjuvant which did have physiological effects on the body and which thereby enhanced the therapeutic effects of the antigen.

18 The Patent Office contends that GSK's action should be dismissed. First of all, it relies on the wording of Article 1(a) and (b) of Regulation No 469/2009, which makes a clear distinction between 'medicinal product' and 'product'. According to the Patent Office, while the former may have an effect on a physiological function, only the latter may in any event be the subject of an SPC. As a consequence, although an adjuvant may fall within the definition of 'medicinal product' within the meaning of Regulation No 469/2009, that does not mean that the adjuvant is an 'active ingredient' or 'product' within the meaning of that regulation. If a substance with general and indirect physiological effects also fell within the concept of 'active ingredient', then it would result in a definition that is too broad and uncertain, leading to divergent results in different Member States.

19 Second, the Patent Office disputes that the main proceedings can be distinguished from those which gave rise to the judgment in *Massachusetts Institute of Technology*. It points out in that regard that, in the grounds of that judgment, the Court made barely any reference to excipients and that neither the ruling nor the reasoning on which it was based was confined to excipients. Thus, the principle established in that judgment and the reasons underlying that principle are directly applicable to a case concerning an adjuvant. Moreover, in that judgment, the Court was required to consider a situation in which the presence of polifeprosan, a polymeric, biodegradable excipient, was necessary to the therapeutic efficacy of the medicinal product. The Patent Office argues that, if inventive merit was the only consideration, the Court would have reached the opposite conclusion.

20 Third, the Patent Office relies on the different definitions of 'active substance' and 'excipient' given by the European Union legislature in Directive 2001/83, as amended by Commission Directive 2003/63/EC of 25 June 2003 (OJ 2003 L 159, p. 46), to demonstrate that an adjuvant cannot be treated in the same way as an active ingredient.

21 The referring court is of the view that, in the light of the arguments put forward by GSK, the answer to issue raised in the main proceedings is not acte clair. That court also observes that, while the competent industrial property offices of Spain, Italy, Luxembourg and Austria have granted GSK SPCs in respect of both AS03 and the combination of an antigen and that adjuvant, on the basis of European Patent (UK) No 0 868 918, the competent Swedish office has refused both SPC applications in question. On the other hand, the Portuguese authorities have refused an SPC in respect of AS03 alone but have granted one in respect of the combination. Finally, the competent Italian and Cypriot authorities have granted SPCs for the combination but, in this instance, on the basis of European Patent (UK) No 1 618 889.

22 In those circumstances, the High Court of Justice (England and Wales), Chancery Division (Patents Court) decided to stay proceedings and refer the following questions to the Court for a preliminary ruling:

'(1) Is an adjuvant which has no therapeutic effect on its own, but which enhances the therapeutic effect of an antigen when combined with that antigen in a vaccine, an "active ingredient" within the meaning of Article 1(b) of Regulation (EC) No 469/2009?

(2) If the answer to question 1 is no, can the combination of such an adjuvant with an antigen nevertheless be regarded as a "combination of active ingredients" within the meaning of Article 1(b) of Regulation (EC) No 469/2009?'

Consideration of the questions referred

23 Pursuant to Article 99 of the Rules of Procedure, where the answer to a question referred to the Court for a preliminary ruling may be clearly deduced from existing case-law or admits of no reasonable doubt, the Court may at any time, on a proposal from the Judge-Rapporteur and after hearing the Advocate General, give its decision by reasoned order.

24 The Court considers that to be the case here, as suggested expressly by the United Kingdom Government and the European Commission and, by implication, the Czech, French and Netherlands Governments, in the light, inter alia, of the judgment in *Massachusetts Institute of Technology*.

25 By its two questions, which it is appropriate to consider together, the referring court asks, in essence, whether Article 1(b) of Regulation No 469/2009 must be interpreted as meaning that, on the one hand, an adjuvant and, on the other, a combination of two substances, namely (i) an active ingredient having therapeutic effects on its own and (ii) an adjuvant which, while enhancing those therapeutic effects, has no therapeutic effect on its own, fall, respectively, within the definitions of 'active ingredient' and 'combination of active ingredients' within the meaning of that provision.

26 It should be recalled that Article 1(b) of Regulation No 469/2009 states that '"product" means the active ingredient or combination of active ingredients of a medicinal product'.
27 In the absence of any definition of the concept of 'active ingredient' in Regulation No 469/2009, the meaning and scope of those terms must be determined by considering the general context in which they are used and their usual meaning in everyday language (see, to that effect, *Massachusetts Institute of Technology*, paragraph 17).
28 In this case, it is important to note that it is generally accepted in pharmacology that the term active 'ingredient' does not include substances forming part of a medicinal product which do not have an effect of their own on the human or animal body (*Massachusetts Institute of Technology,* paragraph 18).
29 It should be pointed out that point 11 of the explanatory memorandum to the proposal for a regulation referred to at paragraph 15 above states that 'product' is to be understood to mean an active substance in the strict sense and that minor changes to the medicinal product such as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the issue of a new SPC. Accordingly, the pharmaceutical form of the medicinal product, to which an excipient may contribute, does not form part of the definition of 'product', which is understood to mean an 'active substance' or 'active ingredient' in the strict sense. Whether a substance without any therapeutic effect of its own is necessary for the therapeutic efficacy of the active ingredient cannot, in this case, be regarded as a sufficiently precise test (see *Massachusetts Institute of Technology*, paragraphs 19 and 21)
30 Accordingly, a substance which does not have any therapeutic effect of its own and which is used to obtain a certain pharmaceutical form of a medicinal product is not covered by the concept of 'active ingredient', which, in turn, is used to define the term 'product' *(Massachusetts Institute of Technology,* paragraph 25).
31 Therefore, the alliance of such a substance with a substance which does have therapeutic effects of its own cannot give rise to a 'combination of active ingredients' within the meaning of Article 1(b) of Regulation No 469/2009 (see, to that effect, *Massachusetts Institute of Technology*, paragraph 26).
32 The fact that the substance without any therapeutic effect of its own renders possible a pharmaceutical form of the medicinal product necessary for the therapeutic efficacy of the substance which does have therapeutic effects cannot invalidate that interpretation *(Massachusetts Institute of Technology*, paragraph 27).
33 It is not unusual for a substance which does not have therapeutic effects of its own to influence the therapeutic efficacy of the active ingredient of a medicinal product (see, to that effect, *Massachusetts Institute of Technology*, paragraph 28).
34 Thus, a definition of 'combination of active ingredients of a medicinal product' which includes a combination of two substances, only one of which has therapeutic effects of its own for a specific indication, the other enhancing the therapeutic effects of the medicinal product, which is necessary for the therapeutic efficacy required of the first substance for that indication, might, on any view, create legal uncertainty in the application of Regulation No 469/2009 (see, to that effect, *Massachusetts Institute of Technology*, paragraph 29).
35 Those considerations also apply to a situation such as that in the main proceedings, in which an adjuvant is in issue which, as it has no therapeutic effects on its own, cannot be regarded as an 'active ingredient' within the meaning of Article 1(b) of Regulation No 469/2009.
36 That distinction between 'active ingredient' and 'adjuvant' is also made quite clear in section 3.2.2.1 of Part 1, entitled 'Standardised marketing authorisation dossier requirements', of Annex I to Directive 2001/83, as amended by Directive 2003/63. That annex lists the particulars and documents to be submitted in support of an MA application in accordance, inter alia, with Article 8(3) of that directive, as amended.
37 Section 3.2.2.1 states as follows:
'A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:
– the active substance(s),
– the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
– the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.).
...'
38 Thus, in Directive 2001/83, as amended by Directive 2003/63, the concepts of 'active substance' and 'adjuvant' are clearly distinct and that also holds, in the context of Regulation No 469/2009, for the concept of 'active ingredient', which cannot, as such, include an adjuvant.
39 It follows from the foregoing that, first, where a patent protects an adjuvant as such – like European Patent (UK) No 0 868 918 – an SPC cannot be granted in respect of that adjuvant, since it cannot be regarded as a 'product' within the meaning of Article 1(b) of Regulation No 469/2009.
40 Second, where a patent, like European Patent (UK) No 1 618 889, protects an active ingredient as such, namely, in the present case, an antigen that is used with an adjuvant, it is true that an SCP may be issued, as suggested by the Patent Office and the referring court, in respect of that 'active ingredient', which permits the holder to enjoy an additional period of exclusivity on the expiry of the basic patent that is intended to compensate, at least in part, for the delay to the commercial exploitation of his invention by reason of

the time which has elapsed between the date on which the application for the patent was filed and the date on which the first MA in the European Union was granted (see **Case C-229/09 Hogan Lovells International [2010] ECR I-11335, paragraph 50**).

41 In such a situation, in accordance with Article 5 of Regulation No 469/2009, an SPC granted in connection with such a product confers, upon the expiry of the basic patent, the same rights as were conferred by that patent in relation to the product, within the limits of the protection conferred by the basic patent, as provided for in Article 4 of the regulation. Accordingly, if, during the period in which that patent was valid, the patent holder could oppose, on the basis of his patent, all use or certain uses of his product in the form of a medicinal product consisting of such a product or containing it, including use with an adjuvant, the SPC granted in relation to that product would confer on the holder the same rights for all uses of the product, as a medicinal product, which were authorised before the expiry of the certificate (see the judgments in **Case C-322/10 Medeva [2011] ECR I-12051, paragraph 39**, and **Case C-422/10 Georgetown University and Others [2011] ECR I-12157, paragraph 32**, and the orders in **Case C-630/10 University of Queensland and CSL [2011] ECR I-12231, paragraph 34**, and Case C-6/11 Daiichi Sankyo [2011] ECR I-12255, paragraph 29).

42 However, such an SPC cannot protect the adjuvant as such, with the result that the SPC would not enable its holder, upon the expiry of the basic patent relied on in support of the application or of a patent protecting the adjuvant as such, to oppose the marketing of a medicinal product containing an active ingredient, other than the active ingredient protected by the SCP, used with that adjuvant.

43 With regard to the judgment in *Neurim Pharmaceuticals (1991)*, it should be noted that in that judgment, as suggested by the Court of Appeal (England and Wales) (Civil Division), the Commission and Advocate General Trstenjak in her Opinion in the case giving rise to that judgment, the Court held, inter alia, at paragraph 24 of the judgment, that, like a patent protecting a 'product' or a patent protecting a process by which a 'product' is obtained, a patent protecting a new application of a new or known product may now, in accordance with Article 2 of Regulation No 469/2009, enable an SPC to be granted and, in that case, in accordance with Article 5 of that regulation, the SPC confers the same rights as conferred by the basic patent as regards the new use of that product, within the limits laid down by Article 4 of that regulation.

44 However, the Court did not, in that judgment, cast doubt on the principle that Article 1(b) of Regulation No 469/2009 is to be interpreted narrowly, as held in the judgment in *Massachusetts Institute of Technology*, to the effect that the term 'product' cannot cover a substance which does not correspond to the definition of 'active ingredient' or that of 'combination of active ingredients'.

45 In the light of all the foregoing considerations, the answer to the questions referred is that Article 1(b) of Regulation No 469/2009 must be interpreted as meaning that, just as 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 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' within the meaning of that provision.

Costs

46 Since these proceedings are, for the parties to the main proceedings, a step in the action pending before the national court, the decision on costs is a matter for that court. Costs incurred in submitting observations to the Court, other than the costs of those parties, are not recoverable.

On those grounds, the Court (Eighth Chamber) hereby rules:

Article 1(b) 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 must be interpreted as meaning that, just as 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 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' within the meaning of that provision.