JUDGMENT OF THE COURT (First Chamber)

18 June 2009 *

In Case C-527/07,

REFERENCE for a preliminary ruling under Article 234 EC from the High Court of Justice of England and Wales, Queen's Bench Division (Administrative Court) (United Kingdom), made by decision of 1 November 2007, received at the Court on 28 November 2007, in the proceedings

The Queen, on the application of:

Generics (UK) Ltd,

v

Licensing Authority, acting through the Medicines and Healthcare products Regulatory Agency,

* Language of the case: English.

supported by:

Shire Pharmaceuticals Ltd,

Janssen-Cilag AB,

THE COURT (First Chamber),

composed of P. Jann, President of the Chamber, A. Tizzano (Rapporteur), A. Borg Barthet, E. Levits and J.-J. Kasel, Judges,

Advocate General: J. Mazák,
Registrar: R. Şereş, Administrator,

having regard to the written procedure and further to the hearing on 27 November 2008,

after considering the observations submitted on behalf of:

— Generics (UK) Ltd, by M. Brealey QC and K. Bacon, Barrister, and by S. Cohen, avocat, instructed by G. Morgan, Solicitor,

— Shire Pharmaceuticals Ltd and Janssen-Cilag AB, by D. Anderson QC and J. Stratford, Barrister, and by P. Bogaert, advocaat, instructed by G. Castle, Solicitor,

— the United Kingdom Government, by V. Jackson, acting as Agent, and J. Coppel and T. de la Mare, Barristers,

— the Polish Government, by M. Dowgielewicz and T. Krawczyk, acting as Agents,

— the Commission of the European Communities, by P. Oliver and M. Šimerdová, acting as Agents,

after hearing the Opinion of the Advocate General at the sitting on 26 March 2009,

gives the following

Judgment

1 This reference for a preliminary ruling concerns the interpretation of Article 10 of 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), as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 (OJ 2004 L 136, p. 34) ('Directive 2001/83').

2 The reference was made in the course of proceedings between Generics (UK) Ltd ('Generics'), a company incorporated under English law which distributes medicinal products, and the Licensing Authority, which is the competent authority in the United Kingdom for issuing marketing authorisations, concerning the lawfulness of the Licensing Authority's decision refusing Generics' application for marketing authorisation for the generic medicinal product galantamine.

The legal framework

3 According to recital 1 in the preamble to Directive 2001/83, that directive codified and assembled in a single text the directives on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products for human use, which included Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (OJ English Special Edition 1965-1966(I) p. 24), as amended by Council Directive 93/39/EEC of 14 June 1993 (OJ 1993 L 214, p. 22) ('Directive 65/65'), Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (OJ 1975 L 147, p. 1), as amended by Commission Directive 1999/83/EC of 8 September 1999 (OJ 1999 L 243, p. 9), and Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ 1975 L 147, p. 13), as amended by Commission Directive 2000/38/EC of 5 June 2000 (OJ 2000 L 139, p. 28) ('Directive 75/319').

4 Recitals 2, 4, 5 and 10 in the preamble to Directive 2001/83 state:

‘(2) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.

…

(4) Trade in medicinal products within the Community is hindered by disparities between certain national provisions, in particular between provisions relating to medicinal products (excluding substances or combinations of substances which are foods, animal feeding-stuffs or toilet preparations), and such disparities directly affect the functioning of the internal market.

(5) Such hindrances must accordingly be removed; whereas this entails approximation of the relevant provisions.

…

(10) However, there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause.’

5 Article 6(1) of that directive provides:

'No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with [Council] Regulation (EEC) No 2309/93 [of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (OJ 1993 L 214, p. 1)].'

6 According to Article 88 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ 2004 L 136, p. 1), Regulation No 2309/93 is repealed and references to that regulation are to be construed as references to Regulation No 726/2004.

7 Article 8 of Directive 2001/83 corresponds, in essence, to Article 4 of Directive 65/65. Article 8(3)(i) of Directive 2001/83 provides:

'The application [for marketing authorisation] shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

…

(i) Results of:

— pharmaceutical (physico-chemical, biological or microbiological) tests,

— pre-clinical (toxicological and pharmacological) tests,

— clinical trials;

…'

8 Article 10(1) and (2) of Directive 2001/83 states:

'1. By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community ["the period of protection"].

…

2. For the purposes of this Article:

(a) "reference medicinal product" shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;

(b) "generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. …'

9 According to Articles 2 and 3 of Directive 2004/27, where the application for authorisation was made before 30 October 2005, the applicable period of protection is that laid down in Article 10 of Directive 2001/83 prior to its amendment by Directive 2004/27. The original wording of Article 10 provided that the period of protection was to be not less than 6 years, but that it was open to each Member State to extend that period of protection up to 10 years.

10 Article 28(1) of Directive 2001/83 states:

'With a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States. The dossier shall contain the information and documents referred to in Articles 8, 10, 10a, 10b, 10c and 11. The documents submitted shall include a list of Member States concerned by the application.

The applicant shall request one Member State to act as "reference Member State" and to prepare an assessment report on the medicinal product in accordance with paragraphs 2 or 3.'

11 According to the Agreement on the European Economic Area of 2 May 1992 (OJ 1994 L 1, p. 3), to which the Republic of Austria was a party before its accession to the European Union, Directive 65/65 and Directive 75/319 were applicable in Austria from 1 January 1994.

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

12 In 1963, the competent Austrian authorities granted to Waldheim, in accordance with the Austrian law in force at the time, marketing authorisation for the medicinal product galantamine, under the brand name 'Nivalin,' for the treatment of poliomyelitis.

13 Although it appears that that authorisation for Nivalin was modified in 1995, in accordance with the applicable Community law, to include its experimental use in the treatment of Alzheimer's disease and, subsequently, to include 'symptomatic treatment' of that illness, it is not in dispute that the original dossier, on the basis of which the marketing of Nivalin was authorised, was — for its part — never updated in accordance with the requirements of Directive 65/65 and Directive 75/319, now applicable in Austria.

14 Waldheim withdrew Nivalin from the market in 2001.

15 Meanwhile, following the conclusion of cooperation agreements with Waldheim, Janssen-Cilag AB submitted to the Swedish competent authorities, pursuant to Article 4 of Directive 65/65 (now Article 8 of Directive 2001/83), a full application for marketing authorisation for galantamine, under the brand name 'Reminyl', for the treatment of Alzeiheimer's disease. After having obtained that authorisation on 1 March 2000, Janssen-Cilag AB also obtained marketing authorisation for Reminyl in Austria on 22 August 2000.

16 In the United Kingdom, Shire Pharmaceuticals Ltd has been the holder of a marketing authorisation for Reminyl since 14 September 2000.

17 On 14 December 2005, in the context of a decentralised procedure pursuant to Article 28(1) of Directive 2001/83, Generics submitted an application to the Licensing Authority for marketing authorisation for a generic of galantamine for the British market. The United Kingdom of Great Britain and Northern Ireland was designated as the reference Member State. Simultaneous applications were lodged in 17 other Member States.

18 That application was submitted on the basis of the generic product exception in Article 10(1) of Directive 2001/83. Nivalin was specified as the reference medicinal product authorised for a period of not less than 10 years in the European Economic Area ('EEA'). The application also mentioned the marketing authorisation obtained in the United Kingdom by Shire Pharmaceuticals Ltd for Reminyl, designated as the reference medicinal product in the United Kingdom, and as the product used for the bioequivalence study necessary to demonstrate that the Generics product was, in fact, a generic of Nivalin/Reminyl.

19 The Licensing Authority rejected Generics' application. It considered that Nivalin, covered by the authorisation issued in Austria, could not be used as the reference medicinal product for an application for marketing authorisation for a generic medicinal product for the purposes of Article 10(1) of Directive 2001/83, since its dossier had not been updated since 1 January 1994 to comply with the requirements of the Community legislation which had become applicable in Austria following the entry

into force of the EEA Agreement. As regards Reminyl, the 10-year period of protection referred to in Article 10 of Directive 2001/83, in its original version, had not yet expired and therefore the authorisation could not be granted on that basis.

20 Generics therefore challenged the Licensing Authority's decision to reject its application before the High Court of Justice of England and Wales, Queen's Bench Division (Administrative Court), which decided to stay proceedings and to refer the following questions to the Court of Justice for a preliminary ruling:

'(1) Where a medicinal product falling outside the scope of the Annex to Regulation [No] 2309/93 has been placed on the market in a Member State ([Republic of] Austria) under its national authorisation procedure prior to the accession of that Member State to the EEA or the [European Community] and:

— that Member State has subsequently acceded to the EEA and then the [European Community], and as part of the conditions of its accession it has transposed into its national law the authorisation provisions of Directive 65/65 (now Directive 2001/83) [on marketing authorisation for medicinal products for human use], no transitional provisions applying in this respect;

— the product in question has remained on the market in that Member State for some years after its accession to the EEA and the [European Community];

— following the accession of that Member State to the EEA and the [European Community], the marketing authorisation for the product in question has been

varied by adding a new indication, and the variation was considered by the authorities of that Member State to be consistent with the requirements of Community law;

— the dossier of the product in question was not updated in accordance with Directive 65/65 (now Directive 2001/83) after that Member State's accession to the EEA and the [European Community]; and

— a product containing the same active ingredient has subsequently been authorised under Article 6 of Directive 2001/83 and placed on the market in the [European Community];

is the medicinal product to be considered to be a "reference medicinal product which is or has been authorised under Article 6 … in a Member State" within the meaning of Article 10(1) of Directive 2001/83 and, if so, which of the above conditions is/are decisive in this respect?

(2) In circumstances where the competent authority of a reference Member State erroneously refuses an application for a marketing authorisation made under Article 10(1) of Directive 2001/83 in the context of the decentralised procedure provided for in that Directive, on the ground that the medicinal product referred to in Question 1 above was not a "reference medicinal product" within the meaning of Article 10(1), what guidance, if any, does the Court of Justice think it appropriate to provide as to which circumstances the national court ought to take into consideration when it comes to determine whether the breach of Community law is a sufficiently serious breach within the meaning of the judgment in [Joined Cases C-46/93 and C-48/93] *Brasserie du Pêcheur and Factortame* [1996] [ECR I-1029]?'

The questions referred

The first question

21 By its first question, the referring court asks, in essence, whether a medicinal product, such as Nivalin in the main proceedings, which falls outside the scope of Regulation No 726/2004, and the placing of which on the market in a Member State was not authorised in accordance with Directive 2001/83, can nevertheless be considered to be a reference medicinal product within the meaning of Article 10(2)(a) of that directive.

22 In order to reply to that question, it should be recalled, at the outset, that the objective of the obligation on applicants seeking marketing authorisation for a medicinal product, to attach to the application the results of toxicological and pharmacological tests, and clinical trials, referred to in Article 8(3)(i) of Directive 2001/83, is to provide proof of the safety and efficacy of a medicinal product (see, to that effect, Case C-440/93 *Scotia Pharmaceuticals* [1995] ECR I-2851, paragraph 17, and Case C-368/96 *Generics (UK) and Others* [1998] ECR I-7967, paragraph 23).

23 It should also be borne in mind that the abridged procedure established by Article 10 of that directive — which relieves applicants seeking marketing authorisation for a generic of a reference medicinal product already authorised in accordance with that directive from having to provide the results of the aforementioned tests and trials — has, inter alia, as its objective, as is apparent from recital 10 in the preamble to Directive 2001/83, to avoid the repetition of tests on humans or animals where not absolutely necessary (*Generics (UK) and Others*, paragraphs 4 and 71).

24 Having regard in particular to the fact that, as is stated in recital 2 in the preamble to Directive 2001/83, the essential aim of any rules governing the production and distribution of medicinal products must be to safeguard public health, the concept of a 'reference medicinal product', within the meaning of Article 10(2)(a) of that directive, cannot be interpreted in such a way that that abridged procedure amounts to a

relaxation of the requirements of safety and efficacy which must be met by medicinal products (see, to that effect, *Scotia Pharmaceuticals*, paragraphs 17 and 22, and *Generics (UK) and Others*, paragraph 22).

25 Thus, in order to be able to grant a marketing authorisation for a generic medicinal product on the basis of the abridged procedure, what matters is that all the particulars and documents relating to the reference medicinal product remain available to the competent authority concerned by the application for authorisation (see, to that effect, Case C-223/01 *AstraZeneca* [2003] ECR I-11809, paragraph 27).

26 If that were not the case, respect for the standards of safety and efficacy which medicinal products must satisfy would be, contrary to the requirements of the case-law referred to in paragraph 24 of this judgment, severely compromised, to the extent that the producers of generic products would be relieved of having to carry out the toxicological and pharmacological tests, and clinical trials, normally required by Community legislation, even though there would be no evidence of the safety and efficacy of the reference medicinal product in question.

27 In other words, it is only in the case where the competent authority has all the particulars and documents relating to the reference medicinal product that Article 10(1) of Directive 2001/83 replaces the obligation on applicants for marketing authorisation to provide results of the tests and trials referred to in Article 8(3)(i) of that directive with the obligation to demonstrate that the medicinal product in question is so similar to that reference medicinal product, which already benefits from such an authorisation, that it does not differ significantly from that product as regards safety and efficacy (see, to that effect, *Generics (UK) and Others*, paragraphs 23 and 24).

28 In that regard, Generics claims, in essence, that a medicinal product placed on the market in a Member State for a number of years in accordance with an authorisation issued on the basis only of the national provisions of that Member State — which were applicable before the transposition in that State of the Community legislation in that

area — may be considered to be a reference medicinal product within the meaning of Article 10(2)(a) of Directive 2001/83.

29 Such an interpretation of Community law is unfounded.

30 It is apparent both from the wording and from the broad logic of Directive 2001/83, in particular from Articles 6, 8 and 10, that only those medicinal products benefiting from a marketing authorisation issued in accordance with that directive can be considered to be reference medicinal products. Likewise, as regards medicinal products for which marketing authorisation was sought prior to the entry into force of that directive, it is clear from the case-law that, in order to benefit from the abridged procedure, the applicant must show that the reference medicinal product was authorised on the basis of the Community law in force at the time of the application for marketing authorisation for the reference medicinal product (see, to that effect, *AstraZeneca*, paragraph 23).

31 Furthermore, any other interpretation of that directive would run counter not only to the requirements of safety and efficacy of the medicinal products and, therefore, the objective of safeguarding public health, but also to the purpose of Directive 65/65 and, subsequently, Directive 2001/83, which — as is apparent from, inter alia, recitals 4 and 5 in the preamble to Directive 2001/83 — is to approximate national laws in the area.

32 Specifically, to allow a medicinal product benefiting from an authorisation issued on the basis of national provisions alone — as applicable in the Member State concerned before the transposition in that State of the aforementioned directives — to be considered to be a reference medicinal product would amount, in fact, to authorising an exception to the rule, laid down in particular in Article 6(1) of Directive 2001/83, that a medicinal product which has not been authorised in accordance with Community law may not be placed on the market of a Member State. As the Advocate General pointed out in points 31 to 34 of his Opinion, there is no provision of that directive which envisages the possibility of such an exception or supports the finding that the mere placing on the market, even for a number of years, of a medicinal product which has not

been the subject of a marketing authorisation issued in accordance with Community law, can replace such authorisation.

33 It follows from the foregoing considerations that, in order that a medicinal product may be considered to be a reference medicinal product, it must have been authorised in accordance with Community law before being placed on the market.

34 In the present circumstances, it is apparent from the file submitted to the Court that Nivalin has never been the subject of an application for marketing authorisation containing the particulars and the documents referred to in Article 8 of Directive 2001/83 and that, therefore, authorisation for it to be placed on the market has never been given in accordance with the requirements of that directive.

35 Likewise, it is not in dispute that Nivalin has also not been the subject of an application for marketing authorisation in accordance with the Community legislation applicable prior to the entry into force of that directive.

36 In actual fact, the placing of Nivalin on the market in Austria was authorised only under the legislation in force in Austria at the time of the granting of the authorisation, namely in 1963, as that authorisation was never updated in accordance with Community law following the accession of the Republic of Austria to the EEA and then the European Union.

37 The answer to the first question therefore is that a medicinal product, such as Nivalin at issue in the main proceedings, which falls outside the scope of Regulation No 726/2004, and the placing of which on the market in a Member State was not authorised in accordance with the applicable Community law, cannot be considered to be a reference medicinal product within the meaning of Article 10(2)(a) of Directive 2001/83.

The second question

38 In the light of the answer given to the first question referred for a preliminary ruling, it is not necessary to answer the second question.

Costs

39 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 (First Chamber) hereby rules:

A medicinal product, such as Nivalin at issue in the main proceedings, which falls outside the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and the placing of which on the market in a Member State was not authorised in accordance with the applicable Community law, cannot be considered to be a reference medicinal product within the meaning of Article 10(2)(a) of 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, as amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004.

[Signatures]