JUDGMENT OF THE COURT (Second Chamber)

9 December 2004 *

In Case C-36/03,

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), made by order of 23 December 2002, received at the Court on 3 February 2003, in the proceedings

The Queen, on the application of:

Approved Prescription Services Ltd,

v

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

interested party:

Eli Lilly & Co. Ltd,

* Language of the case: English.

THE COURT (Second Chamber),

composed of: C.W.A. Timmermans, President of the Chamber, C. Gulmann (Rapporteur), J.-P. Puissochet, N. Colneric and J.N. Cunha Rodrigues, Judges,

Advocate General: F.G. Jacobs,
Registrar: M. Múgica Arzamendi, Principal Administrator,

having regard to the written procedure and further to the hearing on 25 May 2004,

after considering the observations submitted on behalf of:

— Approved Prescription Services Ltd, by J. Mutimear and T. Cook, Solicitors,

— Eli Lilly & Co. Ltd, by I. Dodds-Smith, Solicitor, D. Anderson QC and R. Hugues, Solicitor,

— the United Kingdom Government, by P. Ormond and K. Manji, acting as Agents, and P. Sales and J. Coppel, Barristers,

— the Danish Government, by J. Molde, acting as Agent,

— the French Government, by G. de Bergues and C. Bergeot-Nunes, acting as Agents,

— the Netherlands Government, by H.G. Sevenster, acting as Agent,

— the Commission of the European Communities, by H. Støvlbæk and X. Lewis, acting as Agents,

after hearing the Opinion of the Advocate General at the sitting on 8 July 2004,

gives the following

Judgment

1 The question referred for a preliminary ruling concerns the interpretation of Article 10(1)(a)(iii) 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).

2 The question was raised in proceedings between Approved Prescription Services Ltd ('APS') and the Licensing Authority, acting by the Medicines and Healthcare products Regulatory Agency ('MHRA'), concerning an application for marketing authorisation for a medicinal product.

Legal background

3 Under Article 6(1) of Directive 2001/83, no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued.

4 Article 8(3)(i) of Directive 2001/83 provides:

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

...

(i) Results of:

— physico-chemical, biological or microbiological tests,

— toxicological and pharmacological tests,

— clinical trials.'

5 In the version in force at the time of the facts of the main case, Article 10(1)(a) of Directive 2001/83 provided:

'In derogation of Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property:

(a) The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate:

...

(iii)... that the medicinal product is essentially similar to a medicinal product which has been authorised within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made. ... a Member State may ... extend this period to 10 years by a single Decision covering all the medicinal products marketed on its territory where it considers this necessary in the interest of public health. ...

However, where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate toxicological and pharmacological tests and/or of appropriate clinical trials must be provided.'

6 The procedures laid down in Article 10(1)(a)(i) to (iii) of Directive 2001/83 are commonly known as 'abridged procedures'. The special procedure for obtaining marketing authorisation provided for in the final paragraph of Article 10(1)(a) ('the proviso') is known as a 'hybrid' abridged procedure.

7 The United Kingdom of Great Britain and Northern Ireland has exercised the option granted to the Member States by Article 10(1)(a)(iii) of Directive 2001/83 and has extended the period referred to therein to ten years.

Facts and the question referred for a preliminary ruling

8 The main case concerns three medicinal products, each of them containing the active ingredient Fluoxetine.

9 Two of those medicinal products are produced by Eli Lilly & Co. Ltd ('Eli Lilly'). The first, Prozac capsules, was the first product containing Fluoxetine as an active ingredient to be granted marketing authorisation in the Community. It was authorised in the United Kingdom on 25 November 1988. The second is Prozac liquid, which was first authorised in the Community on 14 October 1992 in

Denmark. Marketing authorisation for Prozac liquid was granted in the United Kingdom on 28 October 1992 following an application made by Eli Lilly under the hybrid abridged procedure. The reference product to which Eli Lilly's application referred was Prozac capsules. When making its application, Eli Lilly conceded that Prozac liquid was not essentially similar to Prozac capsules, on account of its different pharmaceutical form, and submitted additional data intended to show that they were bioequivalent.

10 The third medicinal product in question in the main case, called Fluoxetine liquid 20 mg/5 ml, is produced by APS.

11 In October 1999, APS applied to the MHRA for marketing authorisation for that medicinal product.

12 APS sought to rely on the abridged procedure under Article 10(1)(a)(iii) of Directive 2001/83 on the ground that its product was essentially similar to Prozac liquid. It also stated that the date of first marketing authorisation for its reference medicinal product was 25 November 1988, which is the date on which marketing authorisation for Prozac capsules was granted in the United Kingdom.

13 The MHRA took the view that APS could not use Prozac liquid as a reference product for the purposes of Article 10(1)(a)(iii) of Directive 2001/83 because, at the time when APS made its application, that medicinal product had been authorised in the Community for less than ten years.

14 APS was therefore asked to amend its application so as, this time, to cite as the reference medicinal product Prozac capsules, which had been authorised for more than ten years. According to the MHRA, since that product was not essentially similar to Fluoxetine liquid, APS ought to have applied under the hybrid abridged procedure and supplied additional data in the form of a bioequivalence study comparing the two medicinal products.

15 APS brought an application for judicial review of the MHRA's decision before the High Court, in which it claimed that it was entitled to rely on the data supplied in respect of Prozac liquid.

16 It was against this background that the High Court decided to stay the proceedings and to refer the following question to the Court for a preliminary ruling:

'Can an application for a marketing authorisation for a medicinal Product C validly be made under the first paragraph of Article 10(1)(a)(iii) of Directive 2001/83, where the application seeks to demonstrate that Product C is essentially similar to another product, Product B, in circumstances where:

— Product B is related to an original medicinal Product A, in that Product B has been authorised as a "line extension" of Product A, but has a different pharmaceutical form from Product A or is otherwise not "essentially similar" to Product A within the meaning of Article 10(1)(a)(iii); and

— Product A has been authorised for marketing in the Community for more than the six/ten year period stipulated in Article 10(1)(a)(iii); and

— Product B has been authorised for marketing for less than the six/ten year period stipulated in Article 10(1)(a)(iii)?'

The question referred for a preliminary ruling

17 A medicinal product is essentially similar, within the meaning of Article 10(1)(a)(iii) of Directive 2001/83, to an original medicinal product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent, unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy (Case C-368/96 *Generics (UK) and Others* [1998] ECR I-7967, paragraph 36, concerning an equivalent provision in 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, p. 20).

18 Under Article 10(1)(a)(iii) of Directive 2001/83, where it has been established that a medicinal product is essentially similar to a product which has been authorised within the Community for at least six or ten years and is marketed in the Member State for which the application is made, the applicant is not required to provide the results of toxicological and pharmacological tests or of clinical trials. According to the final paragraph of that provision, 'where the medicinal product is intended for a

different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate toxicological and pharmacological tests and/or of appropriate clinical trials must be provided'.

19 At the hearing, APS, the United Kingdom, Danish, French and Netherlands Governments and the Commission all referred to the judgment of 29 April 2004 in Case C-106/01 *Novartis Pharmaceuticals* [2004] ECR I-4403, which was delivered after they had submitted their written observations but before the hearing. They take the view that it is a necessary implication of the reasoning followed by the Court in that judgment that, in circumstances such as those of the main case, it must be permissible to apply for marketing authorisation for Product C under the abridged procedure even where Product B has been authorised in the Community for less than ten years and even though Products A and B are not essentially similar within the meaning of the Directive because they have a different pharmaceutical form.

20 Eli Lilly, which took the contrary view in its written observations, was not present at the hearing.

21 The Court finds that the position taken by the parties which presented oral argument, namely that the reasoning followed by the Court in *Novartis Pharmaceuticals*, cited above, can be applied to the main case, is well founded.

22 In its judgment in that case, the Court interpreted Article 4.8(a) of Directive 65/65. However, the wording of Article 10(1)(a) of Directive 2001/83 is, essentially, identical to that of Article 4.8(a).

23 The circumstances of the case with which the judgment in *NovartisPharmaceuticals* was concerned were as follows: marketing authorisation had been issued in the United Kingdom for the medicinal Product A more than ten years, and for Product B less than ten years, before the date of the application made for medicinal Product C. The marketing authorisation for Product B had been granted under the hybrid abridged procedure. Products A, B and C were not essentially similar within the meaning of Article 4.8(a) of Directive 65/65 because their bioavailability differed.

24 Referring, in particular, to the proviso, the Court held in, paragraphs 56 to 67 of that judgment, that the applicant for marketing authorisation for Product C may refer to the pharmacological, toxicological and clinical documentation relating to a Product B resulting from the development of the reference Product A, even if Products A and B are not essentially similar on account of their different bioavailability.

25 The Court held that, if an applicant is entitled under the proviso to refer to the data relating to a variant B which differs from the reference medicinal product in the route of its administration or dose, since the differences in those two factors generally imply that products A and B are not bioequivalent, it must, *a fortiori*, likewise be entitled to do so where the two products are distinguishable only by their different bioavailability, even though the route of administration and dose remain unchanged (see *Novartis Pharmaceuticals*, paragraph 66).

26 The same reasoning may be followed where the original medicinal product and the variant differ only in that they have a different pharmaceutical form. Since, as all the parties present at the hearing observed, a new route of administration generally entails a change in pharmaceutical form, the situation to be examined in the main case is analogous to that in *Novartis Pharmaceuticals*.

27 Moreover, as the Advocate General pointed out in paragraphs 14 to 18 and 69 to 73 of his Opinion, this conclusion is supported by the Notice to applicants for marketing authorisations for medicinal products for human use in the Member States of the European Community, which was published by the Commission in 2001.

28 Whilst the United Kingdom Government concurs with the reasoning followed in paragraph 26 of the present judgment, it argues that it also follows from the *Novartis Pharmaceuticals* judgment that, in circumstances such as those of the main case, an applicant for marketing authorisation may refer to the data relating to Product B only if its application is made pursuant to the proviso.

29 It need be stated only that, although the reasoning followed in *Novartis Pharmaceuticals* makes reference to the provision laying down the proviso, it by no means follows that the applicant for marketing authorisation for product C must rely on that provision when making its application.

30 In the light of the foregoing, the answer to the question referred must be that an application for marketing authorisation for a Product C may be made under Article 10(1)(a)(iii) of Directive 2001/83 where the application seeks to demonstrate that Product C is essentially similar to a Product B, in circumstances where:

— Product B is a new pharmaceutical form of Product A, and

— Product A, but not Product B, has been authorised for marketing in the Community for at least the six or ten year period stipulated therein.

Costs

31 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 (Second Chamber) rules as follows:

An application for marketing authorisation for a Product C may be made under Article 10(1)(a)(iii) 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 where the application seeks to demonstrate that Product C is essentially similar to a Product B, in circumstances where:

— **Product B is a new pharmaceutical form of Product A, and**

— **Product A, but not Product B, has been authorised for marketing in the Community for at least the six or ten year period stipulated therein.**

Signatures.