JUDGMENT OF THE COURT (Sixth Chamber)

16 October 2003 *

In Case C-223/01,

REFERENCE to the Court under Article 234 EC by the Østre Landsret (Denmark) for a preliminary ruling in the proceedings pending before that court between

AstraZeneca A/S

and

Lægemiddelstyrelsen,

participant:

Generics (UK) Ltd,

on the interpretation of 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), as amended by Council Directive 93/39/EEC of 14 June 1993 (OJ 1993 L 214, p. 22),

* Language of the case: Danish.

THE COURT (Sixth Chamber),

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

Advocate General: F.G. Jacobs,
Registrar: H. von Holstein, Deputy Registrar,

after considering the written observations submitted on behalf of:

— AstraZeneca A/S, by J. Rothe, advokat, instructed by I. Dodds-Smith, solicitor,

— Generics (UK) Ltd, by N. Lindgreen, advokat, instructed by S. Kon, solicitor,

— the Lægemiddelstyrelsen and the Danish Government, by J. Molde, acting as Agent, and P. Biering, advokat,

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

— the Norwegian Government, by F. Sejersted, acting as Agent,

— the Commission of the European Communities, by H.C. Støvlbæk, acting as Agent,

— the EFTA Surveillance Authority, by E. Wright, acting as Agent,

having regard to the Report for the Hearing,

after hearing the oral observations of AstraZeneca A/S, Generics (UK) Ltd, the Lægemiddelstyrelsen and the Danish Government, the Norwegian Government, the Commission and the EFTA Surveillance Authority at the hearing on 10 October 2002,

after hearing the Opinion of the Advocate General at the sitting on 23 January 2003,

gives the following

Judgment

1 By order of 23 May 2001, received at the Court on 5 June 2001, the Østre Landsret (Eastern Regional Court) referred to the Court for a preliminary ruling under Article 234 EC three questions on the interpretation of 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), as amended by Council Directive 93/39/EEC of 14 June 1993 (OJ 1993 L 214, p. 22) ('Directive 65/65').

2 Those questions were raised in proceedings between AstraZeneca A/S ('AstraZeneca') and the Lægemiddelstyrelsen (Danish agency for medicinal products) concerning the grant of a marketing authorisation for a generic medicinal product to Generics (UK) Ltd ('Generics') under the abridged procedure provided for in Directive 65/65 after the withdrawal of the marketing authorisation of the reference medicinal product.

Legal background

Community law

3 Article 3 of Directive 65/65 provides that no medicinal product may be placed on the market of a Member State unless an authorisation has first been issued by the competent authorities of that Member State in accordance with that 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).

4 Article 4 of Directive 65/65 sets out the procedure to be followed and the documents and particulars which must be provided in order to obtain a marketing authorisation. It establishes both a procedure in which the applicant must provide all the documentation referred to ('the full procedure') and a procedure in which some of that documentation does not have to be provided by the applicant ('the abridged procedure').

5 The first paragraph, and points 8 and 11 of the third paragraph, of that article provide:

'In order to obtain an authorisation to place a medicinal product on the market as provided for in Article 3, the person responsible for placing that product on the market shall make application to the competent authority of the Member State concerned.

...

The application shall be accompanied by the following particulars and documents:

...

8. Results of:

— physico-chemical, biological or microbiological tests,

— pharmacological and toxicological tests,

— clinical trials.

However, 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 pharmacological and toxicological tests or the results of clinical trials if he can demonstrate:

(i) either...;

(ii) or...;

(iii) or that the medicinal product is essentially similar to a 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; this period shall be extended to 10 years in the case of high-technology medicinal products within the meaning of Part A in the Annex to Directive 87/22/EEC... or of a medicinal product within the meaning of Part B in the Annex to that Directive for which the procedure laid down in Article 2 thereof has been followed; furthermore, a Member State may also extend this period to 10 years by a single Decision covering all the products marketed on its territory where it considers this necessary in the interest of public health. Member States are at liberty not to apply the abovementioned six-year period beyond the date of expiry of a patent protecting the original product.

...

...

...

11. Copies of any authorisation obtained in another Member State or in a third country to place the relevant medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 4a or approved by the competent authorities of the Member State in accordance with Article 4b. Copies of the package leaflet proposed in accordance with Article 6 of Directive 92/27/EEC or approved by the competent authorities of the Member State in accordance with Article 10 of the same Directive. Details of any decision to refuse authorisation, whether in the Community or in a third country, and the reasons for such decision.

This information shall be updated on a regular basis.'

6 More specifically, point 8 of the third paragraph of Article 4 of Directive 65/65 was rewritten by Council Directive 87/21/EEC of 22 December 1986 amending Directive 65/65 (OJ 1987 L 15, p. 36).

7 Article 5 of Directive 65/65 provides that marketing authorisation will be refused if, after verification of the particulars and documents listed in Article 4, it proves

that the medicinal product is harmful in the normal conditions of use, or that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or that its qualitative and quantitative composition is not as declared.

8 Chapter Va, entitled 'Pharmacovigilance', of the Second 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 Directive 93/39 ('Directive 75/319'), provides that the Member States are to set up a pharmacovigilance system which, amongst other things, imposes obligations on the holder of a marketing authorisation of a medicinal product regarding the registration and notification of all adverse reactions to that medicinal product in humans. To that end, reports must be submitted to the competent authorities at regular intervals and must be accompanied by a scientific evaluation.

National law

9 Under Paragraph 14(3) of the lov om lægemidler (Law on Medicinal Products), promulgated by Order No 656 of 28 July 1995, and subsequently amended, the Danish Ministry of Health is empowered to lay down the rules to be applied by the Lægemiddelstyrelsen in the examination of applications for marketing authorisation and to determine the particulars which must accompany such applications.

10 In application of that power, bekendtgørelse No 165 om markedsføringstilladelse til lægemidler of 3 March 1995 (Order No 165 on marketing authorisations for medicinal products; 'Order No 165/95') was adopted. Paragraphs 3 to 5 of that

order set out the requirements under the full procedure, and Paragraph 9 sets out the requirements under the abridged procedure.

11 Point 3 of Paragraph 9(1) of Order No 165/95 states as follows:

'Applicants do not need to submit the toxicological, pharmacological and clinical documentation referred to in point 9 of Paragraph 3 if they show that one of the following conditions is satisfied:

...

(3) the medicinal product in respect of which the application is made is essentially identical to a medicinal product which has been approved in the Community, under the Community legislation in force, for at least six years, and marketed in Denmark....'

The dispute in the main proceedings and the questions referred

12 The Astra Group developed a medicinal product in capsule form called 'Losec Entero' ('Losec Entero capsules'). That medicinal product is used in the treatment of gastric-acid ailments. Its active ingredient is Omeprazol. In 1989 the Lægemiddelstyrelsen granted the Astra group a marketing authorisation for that product, which has been marketed in Denmark from that time onwards.

13 On 3 February 1997, AstraZeneca, a company which is incorporated under Danish law and belongs to the Astra group, applied to the Lægemiddelstyrelsen for marketing authorisation of a medicinal product in tablet form, also called 'Losec Entero'. In biological terms, that medicinal product is equivalent to Losec Entero capsules, but the active ingredient is in a different form. The marketing authorisation sought was granted on 22 September 1997.

14 On 23 February 1998, under the abridged procedure provided for in Paragraph 9 of Order No 165/95, Generics applied to the Lægemiddelstyrelsen for marketing authorisation of a medicinal product in capsule form called 'Generics Entero' ('Generics Entero capsules'). That product is a generic medicinal product whose reference medicinal product is Losec Entero capsules.

15 On 6 April 1998, the marketing authorisation for Losec Entero capsules was withdrawn at the request of AstraZeneca. The reasons for its withdrawal were not related to the safety of that product, which continued to be marketed in other Member States.

16 On 30 November 1998, the Lægemiddelstyrelsen granted Generics the marketing authorisation for Generics Entero capsules.

17 On 28 April 1999, AstraZeneca brought an action against that decision before the Østre Landsret. Generics intervened in support of the form of order sought by the Lægemiddelstyrelsen.

18 AstraZeneca has requested that the Lægemiddelstyrelsen be ordered to withdraw the marketing authorisation of Generics Entero capsules on the grounds that, notwithstanding its somewhat ambiguous wording, the Danish version of point 8(a)(iii) of the third paragraph of Article 4 of Directive 65/65 implies, like the English version of that provision, that the marketing authorisation of the reference medicinal product must be in force not only at the time when the application for marketing authorisation of the generic medicinal product is made but also at the time when the marketing authorisation of the generic medicinal product is granted.

19 The Lægemiddelstyrelsen and Generics have submitted that on a proper construction of point 8(a)(iii) of the third paragraph of Article 4 of Directive 65/65, it is necessary and sufficient that the reference medicinal product is covered by a marketing authorisation in force at the time when the application is lodged under the abridged procedure.

20 In those circumstances, the national court has decided to stay proceedings and refer the following questions to the Court for a preliminary ruling:

'(1) In a case where an undertaking applies for marketing authorisation on the basis of an abridged application (simplified procedure) under Article 4, third paragraph, point 8(a)(iii), of the first medicinal products directive (Council Directive 65/65/EEC as subsequently amended) and states that the product for which marketing authorisation is sought is essentially similar to a reference product which has been approved in the Community for the necessary period of time pursuant to the directive, is it necessary and sufficient that the reference product:

(a) at the time of the application has been marketed in the Member State for which the application is made, or

(b) at the time of the application is still being marketed in the Member State for which the application is made, or

(c) is still being marketed at the time of the application and at the time of grant of the marketing authorisation in the Member State for which the application is made?

(2) Does the term "marketed" in Article 4, third paragraph, point 8(a)(iii), mean that it is sufficient and necessary that there be approval in the form of marketing authorisation for the reference product in the Member State for which the application is made?

(3) If Questions 1(b) or 1(c) are answered in the affirmative, does the first medicinal products directive contain a legal basis for enabling the national authorities to dispense with the requirements in question so that an abridged application can nevertheless be examined as to its substance?'

21 By order of 6 June 2002, the national court withdrew point (a) of its first question and its third question.

The questions referred

22 Point 8(a)(iii) of the third paragraph of Article 4 of Directive 65/65 ('the provision at issue') lays down the conditions which must be met by the person

applying for marketing authorisation in order that he be exempted from having to provide the results of pharmacological and toxicological tests or of clinical trials, in other words in order for the abridged procedure to apply.

23 To that end, the applicant must show that

— the medicinal product for which the marketing authorisation is sought is essentially similar to another medicinal product, namely the reference medicinal product;

— the reference medicinal product has been authorised within the Community, in accordance with the Community provisions in force, for at least six or 10 years;

— the reference medicinal product is 'marketed in the Member State for which the application is made'.

24 The national court seeks clarification of that last condition.

25 By its second question, which it is appropriate to examine first, the national court wishes to know whether the words 'product... marketed' used in the provision at issue must be interpreted as meaning that it suffices that the reference medicinal product has been granted a marketing authorisation in the Member State for which the application is made or as meaning that that medicinal product must also actually have been placed on the market in that State.

26 In that regard, as submitted by all the interveners who have expressed their views on that subject to the Court and in line with the Advocate General's analysis in paragraphs 70 to 73 of his Opinion, the Court finds that the words 'product... marketed' must be understood as referring to a medicinal product which has been granted a marketing authorisation.

27 In order to be able to grant a marketing authorisation for a generic medicinal product on the basis of the abridged procedure laid down in the provision at issue, what matters is that all the particulars and documents relating to the reference medicinal product remain available to the competent authority for the Member State where the application for the marketing authorisation is made and not that the reference medicinal product has in fact been placed on the market.

28 This interpretation is, moreover, applied by the Commission in its guidelines on the regulation of medicinal products (published in *The rules governing medicinal products in the European Community*, Volume 2A: *Notice to applicants for marketing authorisations for medicinal products for human use in the Member States of the European Community*, Chapter I, point 4.2.2).

29 The answer to the second question referred to the Court must therefore be that on a proper construction of point 8(a)(iii) of the third paragraph of Article 4 of Directive 65/65, 'product... marketed' refers to a medicinal product which has been granted a marketing authorisation in the Member State concerned.

30 By its first question, the national court seeks clarification as to the time when, for the purposes of an application for marketing authorisation of a generic medicinal product, the reference medicinal product must be 'marketed'.

31 Having regard to the answer to the question relating to the meaning of the words 'product... marketed', the first question in fact seeks to determine the time when, for the purposes of an application for marketing authorisation of a generic medicinal product, the reference product must be 'authorised'.

32 At the outset, it should be noted, first, that it is clear from the wording of the provision at issue that a precondition for application of the abridged procedure is that, at a specific point in time, the reference medicinal product was covered by a marketing authorisation in the Member State in which the application for marketing authorisation of the generic product is made.

33 Second, the problem raised relates to the fact that, in the case at issue in the main proceedings, the marketing authorisation of the reference medicinal product was withdrawn at the request of its holder and that that withdrawal was effected for reasons unrelated to the safety of that product.

34 Several interpretations of the provision at issue have been proposed with regard to the question whether, for the purposes of the abridged procedure, it is necessary for the marketing authorisation of the reference product still to be in force, and if so, until when.

35 On a first interpretation, advocated by Generics, the Netherlands Government and the EFTA Surveillance Authority and based on a line of argument summarised in paragraphs 37 and 38 of the Advocate General's Opinion, it is enough for the reference medicinal product to have been granted a marketing authorisation in the Member State concerned and there is no need for that authorisation still to be in force on the date when the application for marketing authorisation of the generic medicinal product is lodged.

36 On a second interpretation, favoured by the Danish and Norwegian Governments and the Commission, for the reasons set out in paragraphs 39 and 40 of the Advocate General's Opinion, it is necessary and sufficient that the marketing authorisation of the reference medicinal product issued in the Member State concerned be still in force on the date when the application for marketing authorisation of the generic medicinal product is lodged.

37 Finally, on a third interpretation, put forward by AstraZeneca in reliance on the arguments set out in paragraph 36 of the Advocate General's Opinion, it is necessary that the marketing authorisation of the reference medicinal product issued in the Member State concerned be still in force at the time when the marketing authorisation of the generic medicinal product is granted.

38 The Court must consider the merits of each of those interpretations, including the first one, notwithstanding the fact that the national court has withdrawn point (a) of its first question, the aim of which was precisely to ask the Court to rule on the relevance of that interpretation. In the present case, given that the Court is called on to interpret the provision at issue, it is not possible merely to examine some of the possible solutions.

39 In that regard, three general observations should be made.

40 First, the Court has heard submissions pointing out a number of nuances in the wording of the various language versions of the provision in question which the interveners consider should be taken into account.

41 More specifically, in addition to the Danish version of the provision at issue — in the light of which the questions referred for a preliminary ruling were drafted — reference has been made to the German, French and English versions of the provision, which are worded as follows:

'Der Antragsteller ist nicht verpflichtet, die Ergebnisse der pharmakologischen und toxikologischen Versuche oder die Ergebnisse der ärztlichen oder klinischen Versuche vorzulegen, wenn er... nachweisen kann... daß das Arzneimittel im wesentlichen einem Erzeugnis gleicht, das... in dem Mitgliedstaat, in dem der Antrag gestellt wird, in Verkehr gebracht ist.'

'Le demandeur n'est pas tenu de fournir les résultats des essais pharmacologiques et toxicologiques ni les résultats des essais cliniques s'il peut démontrer... que le médicament est essentiellement similaire à un produit... commercialisé dans l'État membre concerné par la demande.'

'The applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate... that the medicinal product is essentially similar to a product which... is marketed in the Member State for which the application is made.'

42 Second, it should be recalled that the abridged procedure established by the provision at issue, which, in certain circumstances, exempts the manufacturers of medicinal products which are essentially similar to already authorised medicinal products from having to provide the results of pharmacological and toxicological tests or of clinical trials, was introduced to enable those manufacturers to save the time and expense needed to gather that data and, in accordance with the fourth recital in the preamble to Directive 87/21, to avoid the repetition of tests on

humans or animals where not absolutely necessary (see, to that effect, Case C-368/96 *Generics (UK) and Others* [1998] ECR I-7967, paragraph 4).

43 However, in laying down the conditions which must be met in order to have recourse to the abridged procedure, the Community legislature also took account of the interests of innovating firms, as is clear from the second recital of Directive 87/21, in particular by making that procedure subject to the condition that the reference medicinal product has been authorised within the Community for six or ten years (see *Generics (UK) and Others*, cited above, paragraphs 72 and 73).

44 Lastly, it is important to bear in mind that Directive 65/65 must be interpreted and applied by reference to its primary purpose, which, as is stated in the first recital to that directive, is to safeguard public health (see, to that effect, *Generics (UK) and Others*, paragraph 22, and Case C-15/01 *Paranova Läkemedel and Others* [2003] ECR I-4175, paragraph 24).

45 A relevant feature of the situation underlying the national court's first question, is, in particular, the fact that the marketing authorisation of the reference medicinal product was withdrawn for reasons unrelated to safety and that after that withdrawal the competent authorities of the Member State concerned did not receive any information that gave rise to doubts as to the characteristics, efficiency or safety of that medicinal product, which is still marketed in other Member States.

46 Those circumstances explain why much of the argument presented to the Court concerns the relevance of the fact that, in principle, after the marketing authorisation of the reference medicinal product has been withdrawn, the holder

of the withdrawn marketing authorisation is no longer bound by the obligations relating to pharmacovigilance laid down in Chapter Va of Directive 75/319 and referred to in paragraph 8 of this judgment.

47 The provision at issue must be interpreted in the light of those considerations in order to determine the time when the marketing authorisation of the reference medicinal product must exist for the purposes of the application for marketing authorisation of a generic medicinal product.

48 First of all, the Court rejects the first potential interpretation, according to which it is enough for the reference medicinal product to have been authorised in the Member State concerned at a given time and there is no need for that authorisation still to be in force on the date when the application for marketing authorisation of the generic medicinal product is lodged.

49 Since the provision at issue must be interpreted in the light of the primary purpose of Directive 65/65, namely the safeguarding of public health, and, as the Advocate General observed in paragraphs 42 and 43 of his Opinion, in accordance with its wording in the majority of the language versions in which it is published, it must be held that by using the present indicative tense the Community legislature intended to require that the marketing authorisation of the reference medicinal product still be in force, at the very least, on the date when the application for marketing authorisation of the generic medicinal product is lodged.

50 However, while it is a necessary condition that the marketing authorisation of the reference medicinal product still be in force on the date when the application for marketing authorisation of the generic medicinal product is lodged, that is also a sufficient condition.

51 That interpretation best reflects the logic and the wording of Articles 4 and 5 of Directive 65/65: Article 4 refers only to the conditions to be met by the application for marketing authorisation and Article 5 provides that authorisation is to be refused if the documents and particulars submitted in support of the application do not comply with the conditions laid down in Article 4.

52 Furthermore, that interpretation best reflects the specific objective of the abridged procedure which, as was pointed out in paragraph 42 of this judgment, is to save the time and expense needed to gather the results of the pharmacological and toxicological tests and clinical trials, and to avoid the repetition of tests on humans or animals.

53 It does not compromise the objective of safeguarding public health pursued by Directive 65/65. In that regard, it should be remembered that application of the abridged procedure may not result in a relaxation of the requirements of safety and efficacy which must be met by medicinal products (see *Generics (UK) and Others*, paragraph 22). Therefore, if the health authorities of the Member State concerned consider, in specific cases and for clearly identified reasons, that the lack of a pharmacovigilance obligation on the holder of the withdrawn marketing authorisation could compromise the safeguarding of public health, they must be able to adopt the appropriate measures, namely, where necessary, they must be able to refuse to use the abridged procedure for granting marketing authorisation of a generic medicinal product.

54 However, such specific cases cannot provide a justification for not, as a general rule, allowing the abridged procedure to be used where the marketing authorisation of the reference medicinal product has been withdrawn for reasons other than those of public health prior to the grant of the marketing authorisation of the generic medicinal product.

55 It should also be noted that, pursuant to the second paragraph of point 11 of the third paragraph of Article 4 of Directive 65/65, the applicant for marketing authorisation of a generic medicinal product is, from the time his application is lodged, under an obligation to update on a regular basis the information contained in the application. As the Commission has pointed out, that means that the applicant must immediately provide the competent authorities with all information on any new matters which may be of importance to the assessment of the product.

56 Furthermore, as the Advocate General observed in paragraphs 56 to 58 of his Opinion, in the period between the application for marketing authorisation of a generic product and the decision to grant that authorisation, the competent authorities have adequate access to information regarding the efficacy and safety of a reference medicinal product which continues to be authorised in other Member States.

57 Moreover, that interpretation of the provision at issue has been advocated by the European Medicines Agencies Co-operation on Legal and Legislative Issues (EMACOLEX), composed of Member State officials specialised in legal affairs, by the European Agency for the Evaluation of Medicinal Products (EMEA) and by the Commission (minutes of the 12th meeting of EMACOLEX, held at Helsinki in November 1999). In addition, the Commission has incorporated that interpretation into its guidelines on the regulation of medicinal products in the European Union, cited above (Chapter I, point 4.2.4).

58 In the light of all the foregoing considerations, the answer to the first question must be that, on a proper construction of point 8(a)(iii) of the third paragraph of Article 4 of Directive 65/65, in order for an application for marketing authorisation of a generic medicinal product to be dealt with by way of the abridged procedure provided for in that provision, it is necessary and sufficient that the marketing authorisation of the reference medicinal product be in force in the Member State concerned on the date of that application.

Costs

59 The costs incurred by the Danish, Netherlands and Norwegian Governments, the Commission and the EFTA Surveillance Authority, which have submitted observations to the Court, are not recoverable. 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.

On those grounds,

THE COURT (Sixth Chamber),

in answer to the questions referred to it by the Østre Landsret by order of 23 May 2001, amended by order of 6 June 2002, hereby rules:

1. **On a proper construction of point 8(a)(iii) of the third paragraph of Article 4 of 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, as amended by Council Directive 93/39/EEC of 14 June 1993, 'product... marketed' refers to a medicinal product which has been granted a marketing authorisation in the Member State concerned.

2. In order for an application for marketing authorisation of a generic medicinal product to be dealt with by way of the abridged procedure provided for in point 8(a)(iii) of the third paragraph of Article 4 of Directive 65/65, as amended, it is necessary and sufficient that the marketing authorisation of the reference medicinal product be in force in the Member State concerned on the date of that application.

Puissochet Schintgen Gulmann

Colneric Cunha Rodrigues

Delivered in open court in Luxembourg on 16 October 2003.

R. Grass V. Skouris

Registrar President