JUDGMENT OF THE COURT (Sixth Chamber)

29 April 2004 *

In Case C-106/01,

REFERENCE to the Court under Article 234 EC by the Court of Appeal (Civil Division) (England and Wales) for a preliminary ruling in the proceedings pending before that court between

The Queen on the application of

Novartis Pharmaceuticals UK Ltd

and

The Licensing Authority established by the Medicines Act 1968 (acting by the Medicines Control Agency),

* Language of the case: English.

and

SangStat UK Ltd,

and

Imtix-SangStat UK Ltd,

on the interpretation of Article 4.8(a) 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 Directives 87/21/EEC of 22 December 1986 (OJ 1987 L 15, p. 36), 89/341/EEC of 3 May 1989 (OJ 1989 L 142, p. 11) and 93/39/EEC of 14 June 1993 (OJ 1993 L 214, p. 22),

THE COURT (Sixth Chamber),

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

Advocate General: F.G. Jacobs,
Registrar: M.-F. Contet, Principal Administrator,

after considering the written observations submitted on behalf of:

— Novartis Pharmaceuticals UK Ltd, by I. Dodds-Smith and R. Hughes, Solicitors, D. Anderson QC, and J. Stratford, Barrister,

— SangStat UK Ltd and Imtix-SangStat UK Ltd, by T. Cook and J. Mutimear, Solicitors,

— the United Kingdom Government, by J.E. Collins, acting as Agent, P. Sales, Barrister and R. Singh QC,

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

— the French Government, by G. de Bergues and R. Loosli-Surrans, acting as Agents,

— the Portuguese Government, by L.I. Fernandes, acting as Agent,

— the Commission of the European Communities, by H.C. Støvlbæk and R. Wainwright, acting as Agents,

having regard to the Report for the Hearing,

after hearing the oral observations of Novartis Pharmaceuticals UK Ltd, SangStat UK Ltd and Imtix-SangStat UK Ltd, the United Kingdom Government, represented by K. Manji, acting as Agent, and P. Sales, the Danish Government, the Netherlands Government, represented by J.G.M. van Bakel, acting as Agent, and the Commission, represented by H.C. Støvlbæk and M. Shotter, acting as Agent, at the hearing on 7 November 2002,

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

gives the following

Judgment

1 By order of 22 February 2001, received at the Court on 5 March 2001, the Court of Appeal (Civil Division) (England and Wales) referred to the Court for a preliminary ruling under Article 234 EC six questions on the interpretation of Article 4.8(a) 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 Directives 87/21/EEC of 22 December 1986 (OJ 1987 L 15, p. 36), 89/341/EEC of 3 May 1989 (OJ 1989 L 142, p. 11), and 93/39/EEC of 14 June 1993 (OJ 1993 L 214, p. 22, hereinafter 'Directive 65/65, as amended').

2 Those questions were raised in proceedings between Novartis Pharmaceuticals UK Ltd ('Novartis') and the Medicines Control Agency ('MCA') concerning the issue by the MCA of two marketing authorisations in respect of a medicinal product.

Law

3 Article 3 of Directive 65/65, as amended, requires a marketing authorisation to be obtained before a medicinal product may be placed on the market in a Member State.

4 Article 4 of the same directive provides:

'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 that the medicinal product is essentially similar to a product authorised in the country concerned by the application and that the person responsible for the marketing of the original medicinal product has consented to the pharmacological, toxicological or clinical references contained in the file on the original medicinal product being used for the purpose of examining the application in question;

...

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.

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 pharmacological and toxicological texts and/or of appropriate clinical trials must be provided.

(b) ...'

5 The procedures established by Article 4.8(a)(i), (ii) and (iii) of Directive 65/65, as amended, are commonly known as 'abridged procedures'. The specific procedure for obtaining marketing authorisation laid down by the last subparagraph of Article 4.8(a) ('the proviso') is known as the 'hybrid' abridged procedure.

6 The United Kingdom has exercised the option conferred on Member States by Article 4.8(a)(iii) of Directive 65/65, as amended, to extend the period referred to therein to 10 years.

7 Lastly, Article 5 of Directive 65/65, as amended, provides:

'The authorisation provided for in Article 3 shall 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.

Authorisation shall likewise be refused if the particulars and documents submitted in support of the application do not comply with Article 4.'

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

8 Sandimmun, Neoral, SangCya and Acceptine are all immuno-suppressants containing the active ingredient cyclosporin. Sandimmun and Neoral are produced by Novartis. SangCya and Acceptine, which may be regarded as identical for the purposes of the present proceedings and are hereinafter referred to collectively as 'SangCya', are produced by SangStat UK Ltd and Imtix-SangStat UK Ltd (hereinafter, collectively, 'SangStat').

9 Cyclosporin is primarily used to prevent rejection of organs or tissues in transplantation surgery. It is also used in the treatment of autoimmune diseases, including severe psoriasis, severe active rheumatoid arthritis, severe nephrotic syndrome and eczema.

10 Sandimmun, Neoral and SangCya are administered to patients orally. They are presented in their final form as a solution, and are taken by the patient in a drink. There are, however, differences between the products. They react differently when diluted for administration to the patient. Sandimmun forms a macroemulsion in an aqueous solution, whilst Neoral forms a microemulsion and SangCya undergoes a process of nanodispersion. That, in turn, has an effect on their bioavailability, that is, the rate and extent of their absorption into the body and of their transfer to the site of action.

11 Bioavailability is important because cyclosporin has a narrow therapeutic index (the dose range within which clinical efficacy is observed with an acceptable safety profile). If the blood levels of cyclosporin in a transplant patient are too low, the risk of acute and chronic organ rejection increases. Conversely, if the levels are too high there is the risk of deteriorating kidney function and the patient's immune system may be suppressed and the patient prone to the development of opportunistic infections and possibly lymphoma. For each of the products, after an initial dose at recommended levels has been given, the actual level of cyclosporin in the blood is monitored in individual patients and the maintenance dosage to be administered to the individual on a long-term basis may be adjusted accordingly to ensure that the level remains within the therapeutic index.

12 Sandimmun was the first cyclosporin product to be authorised within the Community. It was approved in 1983 following the submission by Sandoz Pharmaceuticals (UK) Ltd, now Novartis, of the full file of information required under Directive 65/65, as amended. Consequently, more than 10 years have elapsed since the first marketing authorisation for Sandimmun in the Community, and the 10-year period of data protection afforded to Novartis under the directive has expired. Patent protection in respect of Sandimmun has also expired.

13 Novartis embarked on a research and development programme with a view to producing a more powerful cyclosporin-based product than Sandimmun which would overcome Sandimmun's problems of absorption and administration.

14 Novartis therefore developed the product called Neoral and obtained a patent for the cyclosporin formulation in that product. Neoral first received marketing authorisation within the European Union in Germany on 3 May 1994. Marketing authorisation in the United Kingdom was granted on 29 March 1995. The application made to the Medicines Control Agency ('MCA') as a 'hybrid' abridged application cross-referred, with the consent of the person responsible, to the data relating to Sandimmun, under Article 4.8(a)(i) of Directive 65/65, as amended. However, it also included, under the proviso, data from further studies and clinical trials, in recognition of the fact that Neoral differed in some respects from the reference product. The approved indications for Neoral include all those approved for Sandimmun. In addition, as from January 1997 Neoral has been authorised for the treatment of steroid-dependent or steroid-resistant nephrotic syndrome in adults and children. Sandimmun and Neoral are both available on the market in the United Kingdom, but the former product represents only a small percentage of the total cyclosporin market, as compared with Neoral.

15 Neoral is absorbed into the bloodstream of patients more quickly and consistently than Sandimmun. The influence of concomitant food intake and other variable factors is significantly reduced in Neoral as compared with Sandimmun. Tests have shown that Neoral has approximately 29% higher bioavailability than Sandimmun.

16 On 27 January 1999, the MCA granted two marketing authorisations to SangStat in respect of SangCya by the hybrid abridged procedure under Article 4.8(a)(iii) of Directive 65/65, as amended. The reference product was Sandimmun, which, unlike Neoral, had been authorised in the Community for more than 10 years.

17 SangCya, which was not developed as a copy of Sandimmun or Neoral, is not identical to the latter. It is covered by patent applications and patents granted in the United States of America.

18 SangStat included with its application data to demonstrate the suprabioavailability of SangCya by comparison with Sandimmun and the essential similarity of those products. Studies showing bioequivalence between SangCya and Neoral sold in the United States were also included with the application.

19 For the purposes of granting marketing authorisations for SangCya the MCA also relied on data submitted by Novartis in support of its Neoral application.

20 The national proceedings concern the marketing authorisations granted to SangStat by the MCA in respect of SangCya on 27 January 1999. Novartis applied for judicial review of the decision of the MCA to grant those marketing authorisations, but its application was dismissed.

21 Novartis lodged an appeal before the Court of Appeal seeking to have the contested marketing authorisations set aside. In support of its appeal Novartis submitted that the MCA had:

(a) cross-referred unlawfully to the Neoral file (the cross-reference issue);

(b) erred in finding that SangCya was essentially similar to Sandimmun, thereby exempting SangStat from the requirement to demonstrate that its product was safe notwithstanding its lack of bioequivalence with Sandimmun (the essential similarity issue);

(c) infringed the principle of non-discrimination between Novartis and SangStat in terms of the authorisation procedure (the non-discrimination issue).

22 The MCA contended that:

(a) it was entitled to cross-refer to all information in its possession in assessing whether a product for which marketing authorisation was sought was safe;

(b) questions of essential similarity were inherently questions of fact, degree and expert opinion for the competent national authorities, which enjoy a margin of discretion in deciding issues such as whether two products have the same pharmaceutical form. In any event, bioequivalence is not always required in order to demonstrate essential similarity;

(c) there was no infringement of the principle of non-discrimination since Novartis and SangStat were not in the same position and, in any event, there was an objective and reasonable basis for distinguishing them.

23 In those circumstances the Court of Appeal (Civil Division) (England and Wales) decided to stay the proceedings and to seek a preliminary ruling from the Court of Justice on the following questions:

'1. In considering a marketing authorisation for a new product (C) under Article 4.8(a)(iii) of Directive 65/65, referencing a product (A) authorised more than 6/10 years ago, is a national competent authority ever entitled to cross-refer, without consent, to data submitted in support of a product (B) which was authorised within the last 6/10 years?

2. If so, may such cross-reference be made in circumstances where:

   (a) product B was authorised under the Article 4.8(a) hybrid abridged procedure, referencing product A; and

   (b) the data to which reference is made consists of clinical trials which the national competent authority indicated would be necessary if the marketing authorisation was to be granted and which were submitted in order to demonstrate that product B, though suprabioavailable to product A when administered in the same dose, is safe?

3. (a) Does the final subparagraph of Article 4.8(a) of Directive 65/65 ("the proviso") apply only to applications made under Article 4.8(a)(iii) or to applications made under Article 4.8(a)(i) also?

   (b) Is essential similarity a prerequisite for the use of the proviso?

4. Can products ever be essentially similar for the purposes of Article 4.8(a)(i) and (iii) of Directive 65/65 when they are not bioequivalent, and if so in what circumstances?

5. What is the meaning of the term pharmaceutical form, as used by the Court in its judgment in Case C-368/96 *Generics*? In particular, do two products have

the same pharmaceutical form when they are administered to the patient in the form of a solution diluted to a macroemulsion, microemulsion and nanodispersion respectively?

6. Is it consistent with the general principle of non-discrimination for a national competent authority, faced with hybrid applications for marketing authorisations under Article 4.8(a) of Directive 65/65 referencing product A for two products, neither of which is bioequivalent to product A:

(i) to indicate that it is necessary for a marketing authorisation to be granted for product B to be supported by full clinical data of the type required by Part 4(F) of the Annex to Directive 75/318/EEC; but

(ii) having considered the data filed in support of product B, to grant a marketing authorisation for product C if that application is supported by trials not meeting the requirements of Part 4(F) of the Annex to Directive 75/318/EEC?'

Preliminary remarks

24 Pursuant to Article 4.8(a)(iii) of Directive 65/65, as amended, the applicant is not required to provide the results of pharmacological and toxicological tests or of clinical trials if it is demonstrated that the medicinal product is essentially similar to a product which has been authorised within the Community for at least six or 10 years and marketed in the Member State in respect of which the application is made. According to the final subparagraph 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 pharmacological and toxicological texts and/or of appropriate clinical trials must be provided'.

25 The dispute in the main proceedings concerns, inter alia, the question whether the MCA was entitled by that provision to exempt SangStat from providing such results by basing its decision on the results already provided by Novartis in the course of the procedures resulting in the grant to that company of marketing authorisations for Sandimmun and Neoral.

26 The following factors should be taken into account in relation to that question:

— Neoral and SangCya are not bioequivalent since their bioavailability differs;

— Neoral had been authorised for less than 10 years;

— Neoral is a development of Sandimmun since Novartis obtained marketing authorisation for Neoral under the hybrid abridged procedure.

27 The questions referred for a preliminary ruling ask, more particularly, whether in such circumstances the dispensation from providing the pharmacological, toxicological and clinical documentation applies, as laid down by Article 4.8(a)(iii) of Directive 65/65, as amended, in conjunction with the proviso, or whether

the documentation provided by Novartis in the course of the marketing authorisation procedure for Neoral must be accorded a further period of protection of six or ten years, so that it cannot be used by SangStat in assessing the application for marketing authorisation for SangCya.

28 In Case C-368/96 *Generics and Others* [1998] ECR I-7967, the Court interpreted Article 4.8(a)(iii) of Directive 65/65, as amended, ruling inter alia that:

— the procedure established by that provision enables a second applicant for marketing authorisation for a given product to save the time and expense necessary in order to gather the pharmacological, toxicological and clinical data. In accordance with the fourth recital in the preamble to Directive 87/21, it also avoids, on public policy grounds, the repetition of tests on humans or animals where not absolutely necessary (*Generics*, paragraph 4);

— under the abridged procedure, the obligation to carry out pharmacological, toxicological and clinical tests is replaced by an obligation to show that the medicinal product is so similar to a product which has been authorised for not less than six or ten years in the Community and is marketed in the Member State for which the application is made that it does not differ significantly from that product as regards safety and efficacy, and that it is therefore essentially similar to the product already authorised (*Generics*, paragraph 24);

— a medicinal product is essentially similar, within the meaning of Article 4.8(a)(iii) of Directive 65/65, as amended, 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 (*Generics*, paragraph 36);

— a medicinal product that is essentially similar to a product which has been authorised for not less than six or 10 years and is marketed in the Member State for which the application is made may be authorised, under the abridged procedure, for all therapeutic indications already authorised for that product, even if those indications have been authorised for less than six or 10 years (*Generics*, paragraph 53). The Court stated in this connection that it is, where appropriate, for the Community legislature to adopt measures to reinforce the rules for the protection of innovating undertakings in the harmonised area with which the case is concerned (*Generics*, paragraph 52).

29 It should be added that the Court of Appeal rightly points out in the order for reference that the competent authority of a Member State in making a decision on an application for marketing authorisation must examine the safety and efficacy of the medicinal product, and that it is therefore permissible for that authority to take account of all data in its possession, from whatever source, to the extent that such data demonstrate that the product is harmful or that it lacks efficacy.

30 As stated in the first recital in the preamble to Directive 65/65, as amended, the primary purpose of any rules concerning the production and distribution of medicinal products must be to safeguard public health.

31 Accordingly, and pursuant to the first subparagraph of Article 5 of Directive 65/65, as amended, an application for marketing authorisation must be refused, inter alia, where, on the basis of data in the possession of the competent authority, it appears that a medicinal product is harmful or lacks efficacy. Clearly that authority is not precluded from basing its refusal on data submitted by other applicants, even if that data is protected within the meaning of Article 4.8(a)(iii) of Directive 65/65, as amended.

32 Finally, the Court considers it appropriate to reply, first, to the fourth and fifth questions; second, to the third question; third, to the first and second questions and, lastly, to the sixth question.

The fourth and fifth questions

The fourth question

33 Pursuant to Article 4.8(a)(iii) of Directive 65/65, as amended, as interpreted by the Court, a medicinal product cannot be regarded as essentially similar to an original medicinal product if it does not satisfy 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 (see *Generics*, paragraphs 36 and 37).

34 The same applies in respect of Article 4.8(a)(i) of Directive 65/65, as amended. The two abridged procedures in question are only distinguishable by the fact that the right to refer to the pharmacological, toxicological or clinical documentation contained in the file on the reference medicinal product is dependent, in the first

case, on the consent of the person responsible for the marketing of that medicinal product and, in the second case, on the elapse of six or ten years from the date on which the medicinal product was authorised in the Community.

35 Consequently, the reply to the fourth question must be that products cannot be regarded as essentially similar for the purposes of the application of Article 4.8(a) (i) or (iii) of Directive 65/65, as amended, where they are not bioequivalent.

The fifth question

36 Neither Directive 65/65, as amended, nor, more generally, the Community legislation on medicinal products in force at the time of the facts in the main proceedings, defines the concept of pharmaceutical form.

37 According to the list of reference terms of the European Pharmacopoeia, drawn up under the auspices of the Council of Europe, pharmaceutical form is defined as the combination of the form in which a pharmaceutical product is presented by the manufacturer and the form in which it is administered, including the physical form.

38 Pursuant to the annex to Commission Directive 91/507/EEC of 19 July 1991 modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (OJ 1991 L 270, p. 32), applicants for marketing authorisation are required in several respects to prepare the documentation and information to be submitted pursuant

to Article 4 of Directive 65/65, as amended, in accordance with the requirements set out in the European Pharmacopoeia. In particular, in Part 2, Section E, point 1 of that annex, it is provided, inter alia, that the provisions of the monographs of the European Pharmacopoeia on pharmaceutical forms apply to the products defined therein.

39 In those circumstances, the list of reference terms of the European Pharmacopoeia is capable of providing useful guidelines for the purpose of defining the concept of the pharmaceutical form of a medicinal product in order to address the question whether the medicinal products in question are essentially similar.

40 Consequently, for that purpose, account must be taken of the form in which the pharmaceutical product is presented by the manufacturer and the form in which it is administered, including the physical form.

41 Sandimmun, Neoral and SangCya are presented in the form of a solution to be mixed in a drink for administration to the patient. The fact that, when mixed, these three products form, respectively, a macroemulsion, a microemulsion and a nanodispersion, may provide information as to the form of administration but does not preclude their being treated as having the same pharmaceutical form for the purposes of addressing the question whether they are essentially similar within the meaning of Article 4.8(a)(i) or (iii) of Directive 65/65, as amended, provided that, as the United Kingdom Government and the Commission essentially submit, the differences in the form of administration are not significant in scientific terms.

42 The reply to the fifth question must therefore be that, for the purposes of the procedure laid down by Article 4.8(a)(i) and (iii) of Directive 65/65, as amended, in determining the pharmaceutical form of a medicinal product, account must be taken of the form in which it is presented and the form in which it is administered, including the physical form. In that context, medicinal products such as those at issue in the main proceedings, which are presented in the form of a solution to be mixed in a drink for administration to the patient and which, after mixing, form, respectively, a macroemulsion, a microemulsion and a nanodispersion, are to be treated as having the same pharmaceutical form, provided that the differences in the form of administration are not significant in scientific terms.

The third question

The first part of the third question

43 SangStat and Novartis, and the French and United Kingdom Governments, submit that the proviso applies not only to applications made under Article 4.8(a)(iii) but also to those made under Article 4.8(a)(i).

44 That argument must be upheld.

45 It does not appear that the difference between those two abridged procedures, as identified at paragraph 34 of the present judgment, is such as to justify restricting the hybrid abridged procedure provided for under the proviso to the situation covered by Article 4.8(a)(iii) of Directive 65/65, as amended.

46 It should be noted in this connection that, according to the fourth recital in the preamble to Directive 87/21, there are reasons of public policy for not repeating tests on humans or animals without imperative need. If it is ethically and scientifically inappropriate to repeat all tests for an application which otherwise satisfies all the requirements under Article 4.8(a)(iii) of Directive 65/65, as amended, it is also inappropriate to repeat those tests for an application which otherwise satisfies the requirements set out in Article 4.8(a)(i).

47 Consequently, the reply to the first part of the third question must be that the proviso, that is, the hybrid abridged procedure laid down by the final subparagraph of Article 4.8(a) of Directive 65/65, as amended, applies to applications for marketing authorisation based on Article 4.8(a)(i) or (iii).

The second part of the third question

48 SangStat, the Danish and United Kingdom Governments and the Commission submit that recourse to the proviso is not restricted to cases in which the medicinal product in respect of which marketing authorisation is sought is essentially similar to an authorised product.

49 It should be noted in this regard that according to the express wording of Article 4.8(a)(iii) of Directive 65/65, as amended, relating to the abridged procedure, read in conjunction with the proviso, the essential similarity between the medicinal product in respect of which marketing authorisation is sought and the reference medicinal product is, as the Commission submits, the trigger for the application of the proviso.

50 Thus, the situation covered by the proviso, in which the new medicinal product differs from the reference medicinal product only in terms of its therapeutic indications, covers essentially similar medicinal products, that is, medicinal products having the same qualitative and quantitative composition in terms of active principles and the same pharmaceutical form and which are bioequivalent (*Generics*, paragraphs 36 and 42).

51 By contrast, as SangStat, the Danish and United Kingdom Governments and the Commission stated, the same does not apply in respect of a medicinal product which is to be administered by routes or in doses different from those of the reference medicinal product, since the former generally does not have the same bioavailability as the latter and is not therefore bioequivalent to the reference medicinal product.

52 Accordingly, if recourse to the proviso were only possible where the medicinal product in question is essentially similar to the reference medicinal product and therefore, inter alia, bioequivalent to that product, the proviso would be largely ineffective in the case of medicinal products to be administered by routes or in doses different from those of other medicinal products on the market.

53 Moreover, in the Notice to Applicants for marketing authorisation for medicinal products for human use in the Member States of the European Community, published by the Commission in 1993, it was expressly stated that the proviso could be applied where the new medicinal product did not satisfy the strict criteria for essential similarity when compared with the reference medicinal product.

54 Where the new medicinal product must be administered by routes or in doses different from those of the reference medicinal product, the purpose of the applicant's obligation under the proviso to provide the results of appropriate

pharmacological and toxicological tests and clinical trials is to prove the safety and efficacy of that medicinal product (see, to that effect, *Generics*, paragraph 23).

55 In the light of the foregoing, the reply to the second part of the third question must be that an application for marketing authorisation for a medicinal product may be made under the proviso with reference to an authorised medicinal product provided that the medicinal product in respect of which marketing authorisation is sought is essentially similar to the authorised medicinal product, unless one or more of the differences set out in the proviso apply, as the case may be.

The first and second questions

56 By these two questions, which should be read together, the referring court asks essentially whether, in considering an application for marketing authorisation for a new product C under Article 4.8(a)(iii) of Directive 65/65, as amended, with reference to a product A authorised for more than six or ten years, the competent authority of a Member State is entitled, with a view to granting marketing authorisation, to refer, without the consent of the person responsible for marketing, to data submitted in support of a product B which was authorised within the previous six or ten years under the hybrid abridged procedure of Article 4.8(a) of Directive 65/65, as amended, with reference to product A, where those data consist of clinical trials provided in order to demonstrate that product B, though suprabioavailable to product A when administered in the same dose, is safe.

57 It should be noted that an applicant for marketing authorisation for a medicinal product essentially similar to a product authorised for at least six or 10 years in the Community and marketed in the Member State for which the application is

made is not required, under Article 4.8(a)(iii) of Directive 65/65, as amended, to supply pharmacological, toxicological and clinical documentation for any of the therapeutic indications to which the documentation for the original medicinal product relates, including those authorised for less than six or 10 years (see, to that effect, *Generics*, paragraphs 43 and 44).

58 Thus, the pharmacological, toxicological and clinical documentation covering the new therapeutic indications of a medicinal product already authorised cannot be accorded a further period of protection of six or ten years.

59 The same applies in respect of pharmacological, toxicological and clinical documentation provided for a medicinal product which is to be administered by routes or in doses different from those of other medicinal products on the market.

60 In the light of the proviso, such a medicinal product is a development of the original or reference medicinal product in the same way as a medicinal product intended for a different therapeutic use from that of the original or reference medicinal product.

61 In that context, as stated at paragraph 51 of the present judgment, it is not decisive that a medicinal product to be administered by routes or in doses different from those of the reference medicinal product does not, unlike a medicinal product intended for a therapeutic use different from that of the reference medicinal product, generally satisfy all the criteria for essential similarity.

62 It should be noted in that connection that whether or not the product resulting from the development of the reference medicinal product satisfies all the criteria for essential similarity to the latter product does not necessarily bear any relationship to the cost or difficulty involved in that development.

63 Moreover, if the applicant for marketing authorisation for a medicinal product were only permitted to refer to the pharmacological, toxicological and clinical documentation relating to products resulting from the development of the reference medicinal product where all the criteria for essential similarity are met, it would largely be prevented from referring to that documentation where those products are to be administered by routes or in doses different from those of the reference medicinal product, whilst such reference is permitted where the product is intended for a therapeutic use different from that of the reference medicinal product.

64 Therefore, the applicant for marketing authorisation for a medicinal product may refer to that documentation where the products resulting from the development of the reference medicinal product and the reference medicinal product are essentially similar, apart from the route of administration or the dose, as the case may be.

65 If product B resulting from the development of the reference product A is essentially similar to that reference product, apart from its bioavailability, since that difference is nevertheless not attributable to a difference in the route of administration or the dose, the applicant for marketing authorisation for product C is entitled to refer to the clinical documentation in respect of product B.

66 If, as stated at paragraph 64 of the present judgment, the applicant for marketing authorisation for product C may refer to the pharmacological, toxicological and

clinical documentation in respect of product B, which is the product of the development of the reference product A and essentially similar thereto, apart from the route of administration or the dose, as the case may be, since the differences in those two factors generally imply that products A and B are not bioequivalent (see paragraph 51 of the present judgment), it must, *a fortiori*, be able to do so where products A and B are distinguishable only by their different bioavailability, even though the route of administration and dose remain unchanged.

67 It follows that, in considering an application for marketing authorisation for a new product C under Article 4.8(a)(iii) of Directive 65/65, as amended, with reference to a product A authorised for more than six or ten years, the competent authority of a Member State is entitled, with a view to granting marketing authorisation, to refer without the consent of the person responsible for marketing to data submitted in support of a product B which was authorised within the previous six or ten years under the hybrid abridged procedure laid down by Article 4.8(a) of Directive 65/65, as amended, with reference to product A, where those data consist of clinical trials provided in order to demonstrate that product B, though suprabioavailable to product A when administered in the same dose, is safe.

The sixth question

68 By this question, the Court of Appeal asks whether, in considering two hybrid applications for marketing authorisation for products B and C brought under the proviso and referring to product A, the competent authority of a Member State infringes the principle of non-discrimination if, as a precondition for the grant of marketing authorisation, it requires full clinical data on the bioavailability of

product B, but, having examined the data filed in support of product B, does not require the same data for product C.

69 According to settled case-law, the principle of non-discrimination requires that comparable situations not be treated differently and different situations not be treated in the same way unless such treatment is objectively justified (see, inter alia, Case 106/83 *Sermide* [1984] ECR 4209, paragraph 28, and Case C-137/00 *Milk Marque and National Farmers' Union* [2003] ECR I-7975, paragraph 126).

70 The situation of the applicant for marketing authorisation for product B is, in any event, not comparable to that of the applicant for marketing authorisation for product C. When the latter applicant applies for marketing authorisation, product B is authorised and the authorities are assured of the safety and efficacy of that product.

71 That finding does not prejudge the question whether the competent authority of a Member State is entitled to base its decision on the data filed in support of product B when considering the application for marketing authorisation for product C.

72 Consequently, the reply to the sixth question must be that, in considering two hybrid applications for marketing authorisation for products B and C brought under the proviso and referring to product A, the competent authority of a Member State does not infringe the principle of non-discrimination where, as a

precondition for the grant of marketing authorisation, it requires full clinical data on the bioavailability of product B, but, having examined the data filed in support of product B, does not require the same data for product C.

Costs

73 The costs incurred by the United Kingdom, Danish, French, Netherlands and Portuguese Governments and by the Commission, 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 Court of Appeal (Civil Division) (England and Wales) by order of 22 February 2001, hereby rules:

1. Products cannot be regarded as essentially similar for the purposes of the application of Article 4.8(a)(i) or (iii) 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 Directives 87/21/EEC of 22 December 1986, 89/341/EEC of 3 May 1989, and 93/39/EEC of 14 June 1993, where they are not bioequivalent.

2. For the purposes of the procedure laid down by Article 4.8(a)(i) and (iii) of Directive 65/65, as amended, in determining the pharmaceutical form of a medicinal product, account must be taken of the form in which it is presented and the form in which it is administered, including the physical form. In that context, medicinal products such as those at issue in the main proceedings, which are presented in the form of a solution to be mixed in a drink for administration to the patient and which, after mixing, form, respectively, a macroemulsion, a microemulsion and a nanodispersion, are to be treated as having the same pharmaceutical form, provided that the differences in the form of administration are not significant in scientific terms.

3. The proviso, that is, the hybrid abridged procedure laid down by the final subparagraph of Article 4.8(a) of Directive 65/65, as amended, applies to applications for marketing authorisation based on Article 4.8(a)(i) or (iii).

An application for marketing authorisation for a medicinal product may be made under the proviso, that is, by the abridged hybrid procedure provided for in the final subparagraph of Article 4.8(a) of Directive 65/65, as amended, with reference to an authorised medicinal product provided that the medicinal product in respect of which marketing authorisation is sought is essentially similar to the authorised medicinal product, unless one or more of the differences set out in the proviso apply, as the case may be.

4. In considering an application for marketing authorisation for a new product C under Article 4.8(a)(iii) of Directive 65/65, as amended, with reference to a product A authorised for more than six or ten years, the competent authority of a Member State is entitled, with a view to granting marketing authorisation, to refer without the consent of the person responsible for marketing to data submitted in support of a product B which was authorised within the previous six or ten years under the hybrid abridged procedure laid down by Article 4.8(a) of Directive 65/65, as amended, with reference to product A, where those data consist of clinical trials provided in order to demonstrate that product B, though suprabioavailable to product A when administered in the same dose, is safe.

5. In considering two hybrid applications for marketing authorisation for products B and C brought under the final subparagraph of Article 4.8(a) of Directive 65/65, as amended, and referring to product A, the competent authority of a Member State does not infringe the principle of non-discrimination where, as a precondition for the grant of marketing authorisation, it requires full clinical data on the bioavailability of product B, but, having examined the data filed in support of product B, does not require the same data for product C.

Skouris Gulmann Cunha Rodrigues

Puissochet Schintgen

Delivered in open court in Luxembourg on 29 April 2004.

R. Grass V. Skouris

Registrar President