JUDGMENT OF THE COURT (Fifth Chamber)
3 December 1998 *

In Case C-368/96,

REFERENCE to the Court under Article 177 of the EC Treaty by the High Court of Justice of England and Wales, Queen's Bench Division, for a preliminary ruling in the proceedings pending before that court between

The Queen

and

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

ex parte **Generics (UK) Limited,**

intervener: **E. R. Squibb & Sons Limited,**

between

The Queen

and

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

* Language of the case: English.

ex parte **The Wellcome Foundation Limited,**

and between

The Queen

and

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

ex parte **Glaxo Operations UK Limited and Others,**

intervener: **Generics (UK) Limited,**

on the interpretation and validity of Article 4.8(a)(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 (OJ, English Special Edition 1965-1966, p. 20), as amended by Council Directive 87/21/EEC of 22 December 1986 (OJ 1987 L 15, p. 36),

THE COURT (Fifth Chamber),

composed of: J.-P. Puissochet, President of the Chamber, J. C. Moitinho de Almeida, C. Gulmann (Rapporteur), L. Sevón and M. Wathelet, Judges,

Advocate General: D. Ruiz-Jarabo Colomer,
Registrar: H. von Holstein, Deputy Registrar,

after considering the written observations submitted on behalf of:

— Generics (UK) Limited, by Gerald Barling QC and David Anderson, Barrister, instructed by Stephen Kon, Solicitor,

— The Wellcome Foundation Limited and Glaxo Operations UK Limited and Others, by Geoffrey Hobbs QC and Jemima Stratford, Barrister, instructed by Trevor Cook and Sarah Faircliffe, Solicitors,

— E. R. Squibb & Sons Limited, by Christopher Clarke QC and Nicholas Green, Barrister, instructed by Ian Dodds-Smith and Alison Brown, Solicitors,

— the United Kingdom Government, by John E. Collins, Assistant Treasury Solicitor, acting as Agent, David Pannick QC and Dinah Rose, Barrister,

— the Danish Government, by Peter Biering, Head of Division at the Ministry of Foreign Affairs, acting as Agent,

— the French Government, by Catherine de Salins, Head of Subdirectorate in the Directorate for Legal Affairs at the Ministry of Foreign Affairs, and Régine Loosli-Surrans, Chargé de Mission in the same directorate, acting as Agents,

— the Swedish Government, by Eric Brattgård, Departementsråd in the Department of Foreign Trade of the Ministry of Foreign Affairs, acting as Agent,

— the Norwegian Government, by Ingvald Falch, Advocate in the office of the Attorney-General, acting as Agent,

— the Council of the European Union, by Maria Cristina Giorgi, Legal Adviser, and Aidan Patrick Feeney, of its Legal Service, acting as Agents, and

— the Commission of the European Communities, by Richard Wainwright, Principal Legal Adviser, and Fernando Castillo de la Torre, of its Legal Service, acting as Agents,

having regard to the Report for the Hearing,

after hearing the oral observations of Generics (UK) Limited, The Wellcome Foundation Limited and Glaxo Operations UK Limited and Others, E. R. Squibb & Sons Limited, the United Kingdom Government, the French and Norwegian Governments, the Council and the Commission at the hearing on 11 December 1997,

after hearing the Opinion of the Advocate General at the sitting on 22 January 1998,

gives the following

Judgment

1 By order of 10 October 1996, received at the Court on 22 November 1996, the High Court of Justice, Queen's Bench Division, referred to the Court for a preliminary ruling under Article 177 of the EC Treaty several questions on the interpretation and validity of Article 4.8(a)(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 (OJ, English Special Edition 1965-1966, p. 20), as amended by Council Directive 87/21/EEC of 22 December 1986 (OJ 1987 L 15, p. 36).

2 Those questions were raised in three sets of proceedings between Generics (UK) Limited ('Generics'), The Wellcome Foundation Limited ('Wellcome'), and Glaxo Operations UK Limited and Others ('Glaxo'), on the one hand, and the Licensing Authority established by the Medicines Act 1968 (represented by The Medicines Control Agency ('the MCA')), on the other, concerning, as regards the first dispute, the MCA's refusal to grant, under the procedure provided for in Article 4.8(a)(iii) of Directive 65/65 (hereinafter 'the provision at issue'), a marketing authorisation for a medicinal product known as 'captopril' and, as regards the other two disputes, the grant to competing undertakings, under that procedure, of a marketing authorisation for medicinal products known as 'aciclovir' and 'ranitidine', respectively.

3 Article 4 of Directive 65/65, as amended by Directive 87/21, 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;

(ii) or by detailed references to published scientific literature presented in accordance with the second paragraph of Article 1 of Directive 75/318/EEC that the constituent or constituents of the medicinal product have a well established medicinal use, with recognised efficacy and an acceptable level of safety;

(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) ...'

4 The abridged procedure established by that provision in the cases referred to in subparagraphs (i), (ii) and (iii) 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.

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

6 Annex II to Commission Regulation (EC) No 541/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation granted by a competent authority of a Member State (OJ 1995 L 55, p. 7) provides that certain changes to a marketing authorisation, a list of which is set out in that Annex, are to be considered to fundamentally alter the terms of that authorisation and therefore to require an application for a new marketing authorisation to be made, and not merely an application to vary the terms of the marketing authorisation. Amongst the changes which require a new application are, *inter alia*, the addition of an indication in a different therapeutic area, the addition of a new strength and the addition of a new route of administration.

7 Captopril is a medicinal product developed by Bristol-Myers Squibb Pharmaceuticals Limited ('BMS') in the 1970s. The first marketing authorisation for it was granted in Germany on 23 January 1981. On 27 March 1981 E. R. Squibb & Sons Limited ('Squibb'), a subsidiary of BMS, obtained a marketing authorisation for captopril in the United Kingdom. Captopril was originally indicated for the treatment of severe hypertension. Following research by BMS relating to captopril, which involved substantial costs, new marketing authorisations were granted in the United Kingdom for new therapeutic indications.

8 Generics carries on its business activities in the United Kingdom as a manufacturer and distributor of generic medicinal products. On 20 January 1993 it submitted to the MCA, under the provision at issue, an abridged application for a marketing authorisation for captopril. The MCA granted it marketing authorisations for captopril in respect of indications which had been authorised in any Member State of the European Union for not less than 10 years but refused to grant it marketing authorisations for any indications which had not been approved for at least 10 years. Generics therefore applied to the High Court of Justice for judicial review of that decision.

9 The MCA then informed Generics that it had decided that when the holder of the original marketing authorisation had added a new indication during the preceding 10 years such that a new application would be required under Annex II to Regula-

tion No 541/95 and that change had been the subject of a new marketing authorisation or had been incorporated into the original marketing authorisation, then protection of new data submitted in support of the change would be given for a period of 10 years. The MCA stated that a second applicant could refer to original data pursuant to Article 4.8(a)(iii) of Directive 65/65, as amended, for changes which did not satisfy the criteria laid down in Annex II to Regulation No 541/95.

10 The MCA therefore informed Generics that it was merely refusing to grant, under the abridged procedure, marketing authorisations in respect of indications for captopril which had been added over the last 10 years and which satisfied the criteria under which a change to an authorisation required a new application under Annex II to Regulation No 541/95. That was the case in respect of the indication for diabetic nephropathy. On the other hand, the MCA accepted that Generics could use the abridged procedure in respect of the indication for myocardial infarction, which, although added less than 10 years previously, did not satisfy the criteria under which a change to an authorisation required a new application under Annex II.

11 Wellcome holds all the marketing authorisations granted for aciclovir in the United Kingdom between 1981 and 1994. During that period Wellcome incurred considerable expenditure, particularly on the development of new indications, dosage forms and routes of administration. On 29 February 1996 A/S Gea Farmaceutisk Fabrik ('Gea') obtained marketing authorisations for all the therapeutic indications and dosage forms of aciclovir tablets and intravenous infusion aciclovir for which Wellcome had obtained authorisation in the United Kingdom at that date.

12 Wellcome took the view that the decision to grant marketing authorisations to Gea had been taken in accordance with the new position adopted by the United Kingdom authorities regarding the application of Article 4.8(a)(iii) of Directive 65/65, as amended, and lodged an application for judicial review of the MCA's decision to grant Gea marketing authorisations under the abridged procedure in respect of therapeutic indications, routes of administration and dosage forms for aciclovir tab-

lets and intravenous infusion which had been approved in the Community for less than 10 years.

13 Glaxo obtained all marketing authorisations for ranitidine granted in the United Kingdom between 1981 and 1995 after incurring significant expenditure on research and development. Following the submission by Generics of an abridged application for marketing authorisation in respect of ranitidine tablets of 150 mg and 300 mg, Glaxo wrote to the MCA on 15 April 1996 seeking assurances that its right to protection of its own data would be respected. In reply the MCA stated that it considered that subsequent applications for marketing authorisations for products containing ranitidine could rely on the provision at issue for all the indications listed in Glaxo's letter of 15 April 1996. That letter referred to ranitidine tablets of 150 mg and 300 mg for all authorised recommended indications, doses and dosage schedules.

14 Glaxo applied to the national court for judicial review of the MCA's decision in respect of indications, doses and dosage schedules for ranitidine tablets which had been the subject of marketing authorisations granted less than 10 years previously.

15 The innovative pharmaceutical companies consider, in essence, that the abridged procedure in question may be applied only if the applicant shows not only that the composition of the product for which it has applied for a marketing authorisation is comparable to the original product which has been authorised for not less than 10 years, but also that each therapeutic indication, dose, dosage form or dosage schedule for which the marketing authorisation has been applied for has been authorised for not less than 10 years.

16 Generics takes the view that if the applicant is able to show that the composition of the product for which he is requesting a marketing authorisation is essentially similar to that of an original product which has been authorised for not less than 10 years, he may obtain, under the abridged procedure, a marketing authorisation for any indication, dose, dosage schedule or form of dosage for which the original

product was authorised, irrespective of when the marketing authorisation was changed or the new marketing authorisation was granted.

17 According to the MCA, Article 4.8(a)(iii) of Directive 65/65, as amended, must be interpreted as meaning that where the applicant shows that the composition of the product for which he is seeking marketing authorisation is essentially similar to that of the original product, he may, under the abridged procedure, obtain a marketing authorisation for both the original indications, dosage schedules, doses or dosage forms and any addition or change to the indications, dosage schedules, doses or dosage forms for which the original product was authorised, whether or not during the last 10 years, save where those additions or changes constitute major therapeutic innovations. The MCA considers that this is the case where a new application for marketing authorisation is required under Annex II to Regulation No 541/95. In such a case, marketing authorisation under the abridged procedure cannot be granted in respect of additions or changes that are the subject of a first marketing authorisation until a period of 10 years has elapsed since the date on which it was granted.

18 In that context, the High Court of Justice decided to stay proceedings and to refer the following questions to the Court of Justice for a preliminary ruling:

' (1) (a) What is meant by "essentially similar" for the purposes of Article 4.8(a)(iii) of Council Directive 65/65/EEC (as amended)? In particular, when seeking to establish for that purpose that a medicinal product (product B) is essentially similar to a medicinal product which has been authorised within the Community for 6 or 10 years in accordance with the Community provisions in force (product A), by reference to which physical or other characteristics or attributes of the medicinal products in question should this be determined?

(b) Does the competent authority of a Member State have a margin of discretion in determining the criteria in accordance with which the question of whether product B is essentially similar to product A is to be judged, and if so to what extent?

(2) May product B be authorised in accordance with Article 4.8(a)(iii) of Directive 65/65/EEC (as amended) in respect of:

(a) all indications for which product A is currently authorised in the relevant Member State at the date of the application made in relation to product B; or

(b) only those indications for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years; or

(c) only:

(1) those indications for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years; and

(2) those indications for which product A has been authorised for a shorter period, and which did not require an application for the grant of a new marketing authorisation under the provisions of Annex II of Commission Regulation 541/95 or (as the case may be) would not have required such an application had the said regulation been in force at the time the indication in question was added by variation to an existing authorisation; or

(d) some other category of indications, and if so which?

(3) May product B be authorised in accordance with Article 4.8(a)(iii) of Directive 65/65/EEC (as amended) in respect of:

(a) all dosage forms and/or doses and/or dosage schedules for which product A is currently authorised in the relevant Member State at the date of the application made in relation to product B; or

(b) only those dosage forms and/or doses and/or dosage schedules for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years; or

(c) only:

(1) those dosage forms and/or doses and/or dosage schedules for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years; and

(2) those dosage forms and/or doses and/or dosage schedules for which product A has been authorised for a shorter period, and which did not require an application for the grant of a new marketing authorisation under the provisions of Annex II of Commission Regulation 541/95 or (as the case may be) would not have required such an application had the said regulation been in force at the time the dosage form and/or dose and/or dosage schedule in question was added by variation to an existing authorisation; or

(d) some other category of dosage forms and/or doses and/or dosage schedules, and if so which?

(4) Does it make any difference to the answer to Questions 2 and/or 3 whether the original or abridged applications for marketing authorisations were made before 16 March 1995, the date upon which Commission Regulation 541/95 entered into force?

(5) In the light of the answers to Questions 1 to 4 above, is Article 4.8(a)(iii) invalid as contrary to the principles of protection of innovation and/or non-discrimination and/or proportionality and/or respect for property?'

The first question

19 By its first question, the national court is asking the Court to give a ruling on the criteria which a medicinal product must satisfy in order that it may be regarded, for the purposes of Article 4.8(a)(iii) of Directive 65/65 (as amended), as essentially similar to a product which has already been authorised in a Member State. It also asks whether a Member State has a margin of discretion when determining those criteria.

20 The provision at issue allows the abridged procedure to be used where the medicinal product for which marketing authorisation is sought is essentially similar to a product which has been authorised within the Community, in accordance with the Community provisions in force, for not less than 6 or 10 years and is marketed in the Member State for which the application is made.

21 Directive 65/65 does not define the concept of an essentially similar medicinal product.

22 Having regard in particular to the fact that, as is stated in the first recital in the preamble to Directive 65/65, the primary purpose of any rules concerning the production and distribution of medicinal products must be to safeguard public health, the concept of an essentially similar medicinal product cannot be interpreted in such a way that the abridged procedure, and in particular that laid down in Article 4.8(a)(iii), amounts to a relaxation of the requirements of safety and efficacy which must be met by medicinal products (see, to that effect, Case C-440/93 *Scotia Pharmaceuticals* [1995] ECR I-2851, paragraph 17).

23 That procedure is merely intended to reduce the time needed to prepare an application for authorisation by freeing the applicant from the obligation to carry out the pharmacological and toxicological tests and clinical trials referred to in Article 4.8 of Directive 65/65, the objective of which is to prove the safety and efficacy of medicinal products (see *Scotia Pharmaceuticals*, cited above, paragraph 17).

24 Consequently, under the procedure provided for in Article 4.8(a)(iii) the obligation to carry out those 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 6 or 10 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.

25 It should be noted in that regard that, according to the minutes of the meeting of the Council in December 1986 at which Directive 87/21 was adopted, the criteria determining the concept of essential similarity between medicinal products are that they have the same qualitative and quantitative composition in terms of active principles and the same pharmaceutical form, and, where necessary, bioequivalence of the two products has been established by appropriate bioavailability studies.

26 According to the case-law of the Court, a declaration recorded in the minutes of the Council on the occasion of the adoption of a directive cannot be used for the purpose of interpreting a provision of that directive where no reference is made to the content of the declaration in the wording of the provision in question (Case C-292/89 *Antonissen* [1991] ECR I-745, paragraph 18, and Case C-329/95 *VAG Sverige* [1997] ECR I-2675, paragraph 23).

27 However, inasmuch as it serves to clarify a general concept such as that of an 'essentially similar medicinal product', as used in particular in Article 4.8(a)(iii) of Directive 65/65 (as amended), a declaration of that kind may be taken into consideration when interpreting that provision.

28 The definition of that concept adopted in the minutes of the Council is, moreover, used in the guidelines published by the Commission in *The rules governing medicinal products in the European Community*, Volume II: *Notice to applicants for marketing authorisations for medicinal products for human use in the Member States of the European Community*. According to the Annex to Council Directive 75/318/EEC of 20 May 1975 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 1975 L 147, p. 1), as amended by Commission Directive 91/507/EEC of 19 July 1991 (OJ 1991 L 270, p. 32), the particulars and documents accompanying an application for marketing authorisation pursuant to Article 4 of Directive 65/65 are to be presented in a way which, *inter alia*, takes account of those rules.

29 The Danish, French and Norwegian Governments and the Commission have submitted that the three criteria set out in paragraph 25 of this judgment determine whether a medicinal product is 'essentially similar'. According to the United Kingdom Government, the application of those three criteria constitutes a guarantee that two given medicinal products are essentially similar as regards their physical characteristics.

30 As regards the criterion of bioequivalence, according to the Annex to Directive 75/318, as amended by the Annex to Directive 91/507, an assessment of bioavailability is to be undertaken where necessary to demonstrate bioequivalence for the medicinal products referred to in Article 4.8(i), (ii) and (iii) of Directive 65/65.

31 The 1996 edition of the Commission's *Rules governing medicinal products in the European Union*, Volume III, Part 2: *Guidelines on the quality, safety and efficacy of medicinal products for human use*, to which the Commission refers in its observations, states that 'two medicinal products are bioequivalents if they are pharmaceutical equivalents or alternatives and if their bioavailabilities (rate and extent) after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same', (pp. 505 and 506). The same definition is used in the latest edition of the Commission's *Rules governing medicinal products in the European Union*, Eudralex, Volume 3C, Guidelines on medicinal products for human use, Efficacy, 1998 Edition, p. 234).

32 However, according to the Commission's observations and, in particular, the latest edition of its *Rules governing medicinal products in the European Union* (p. 235), a medicinal product which satisfies the three criteria referred to in paragraph 25 of this judgment may nevertheless raise questions of safety related to its excipients.

33 In such a case, the medicinal product cannot be regarded as essentially similar to the original product.

34 That is so whenever it is apparent that a medicinal product which has the same qualitative and quantitative composition in terms of active principles and the same pharmaceutical form as the original medicinal product, and which is bioequivalent

to that product, nevertheless differs significantly from that product as regards safety or efficacy.

35 In those circumstances, it must be held that the three criteria set out in the minutes of the Council may serve to define the concept of essential similarity, save where it is apparent in the light of scientific knowledge that the medicinal product satisfying those criteria differs significantly from the original product as regards safety or efficacy.

36 Having regard to the foregoing, the answer to the first part of the first question must be that Article 4.8(a)(iii) of Directive 65/65, as amended, is to be interpreted as meaning that a medicinal product is essentially similar 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.

37 As regards the second part of the first question, it follows from the foregoing considerations that the competent authority of a Member State may not disregard the three criteria set out above when it is required to determine whether a particular medicinal product is essentially similar to an original medicinal product.

The second question

38 By its second question, the national court is seeking in essence to ascertain what therapeutic indications may be authorised under the abridged procedure provided

for in Article 4.8(a)(iii) of Directive 65/65, as amended, in respect of a medicinal product that is essentially similar to a medicinal product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made.

39 As already stated in paragraphs 20 and 24 of this judgment, where it has been shown that a medicinal product is essentially similar to a product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made, the applicant is not required, under the provision at issue, to provide results of pharmacological and toxicological tests or of clinical trials.

40 In such a situation, the competent authority for the grant of marketing authorisation uses the pharmacological, toxicological and clinical documentation relating to the original medicinal product. That documentation may, *inter alia*, cover both the therapeutic indications of the original product which has been authorised for not less than 6 or 10 years in the Community and more recent therapeutic indications.

41 In the context of the abridged procedure at issue in the main proceedings, it must therefore be asked whether the dispensation, granted to the applicant for marketing authorisation, from providing pharmacological, toxicological and clinical documentation means that a marketing authorisation may be granted to the applicant in respect of all therapeutic indications covered by the pharmacological, toxicological and clinical documentation relating to the original product, or whether the documentation concerning indications that have been authorised for less than 6 or 10 years, or at least some of them, enjoys a period of independent protection.

42 In this respect it should be noted that having the same therapeutic indications is not one of the criteria which, according to paragraph 36 of this judgment, must be satisfied in order that two medicinal products may be regarded as essentially similar.

43 It follows that an applicant for marketing authorisation for a medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made is not required, under the provision at issue, to supply pharmacological, toxicological and clinical documentation, whatever be the therapeutic indications to which the documentation for the original medicinal product relates.

44 Consequently, under the abridged procedure provided for in Article 4.8(a)(iii) of Directive 65/65, as amended, the applicant may receive marketing authorisation for all therapeutic indications covered by the latter documentation, including those indications authorised for less than 6 or 10 years.

45 The Commission submits that, having regard to the fact that the general purpose of the provision at issue is to ensure fair protection for innovation, it should be possible in the exceptional circumstances of major therapeutic innovation — essentially where there is an entirely new therapeutic indication — to protect the results of new pharmacological and toxicological tests and clinical trials relating to the reference product in their turn in the same way as for any new medicinal product.

46 The Commission indeed proposes that therapeutic indications representing a major therapeutic innovation requiring full new pharmacological or toxicological tests or clinical trials should be given independent protection. It submits that regard may be had to the fact:

— that the major therapeutic innovation is, in the opinion of the European Agency for the Evaluation of Medicinal Products, of significant therapeutic interest within the meaning of the third paragraph of Part B of the Annex to 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), or

— that the innovation has been patented under the Munich Convention on the grant of European Patents or under the applicable national legislation.

47 Clearly, however, to grant an autonomous period of protection to pharmacological, toxicological and clinical documentation covering certain therapeutic indications in respect of the original medicinal product is, as is apparent from paragraphs 42 to 44 of this judgment, contrary to the wording of the provision at issue, interpreted in the light of the definition of what constitutes an essentially similar medicinal product.

48 Furthermore, the diverse nature of the criteria proposed by the Commission in order to determine which therapeutic indications constitute a major therapeutic innovation means that the concept of 'major therapeutic innovation' is insufficiently precise. In the circumstances, application of those criteria would in any event tend to undermine the principle of legal certainty.

49 The United Kingdom Government submits that the criterion of a fundamental change to the terms of a marketing authorisation for a medicinal product, referred to in Appendix II to Regulation No 541/95, allows a distinction to be drawn between simple changes which do not require any additional protection and changes of great therapeutic significance for which a new period of protection is necessary.

50 The United Kingdom's argument is, however, subject to the same objections as those set out in paragraph 47 above.

51 Moreover, for the reasons given by the Advocate General in point 62 of his Opinion, in particular the fact that Annex II to Regulation No 541/95 states that it is without

prejudice to the provisions of Article 4 of Directive 65/65 and that that regulation does no more than harmonise administrative practices applicable to changes in the terms of marketing authorisations, the argument cannot be upheld.

52 That being the case, there is no dispute 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 present case is concerned.

53 Having regard to the foregoing, the answer to the second question must be that a medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years and is marketed in the Member State for which the application is made may be authorised, under the abridged procedure provided for in Article 4.8(a)(iii) of Directive 65/65, as amended, for all therapeutic indications already authorised for that product.

The third question

54 By its third question, the national court is asking essentially what dosage forms, doses and dosage schedules may be authorised under Article 4.8(a)(iii) of Directive 65/65, as amended, for a medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made.

55 Assuming that the terms dosage form, dose and dosage schedule as used by the national court do not preclude essential similarity between the medicinal products

in accordance with the definition adopted in paragraph 36 of this judgment, the third question is identical, *mutatis mutandis*, to the second question.

56 Consequently, having regard to the arguments set out in the context of the second question and the answer to that question, the answer must be that a medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made may be authorised under the abridged procedure provided for in Article 4.8(a)(iii) of Directive 65/65, as amended, for all dosage forms, doses and dosage schedules already authorised for that product.

The fourth question

57 By this question, the national court asks in essence whether the fact that the original or abridged applications for marketing authorisations were made before the date on which Regulation No 541/95 entered into force affects the answers to the second and third questions.

58 It is clear from the foregoing that Regulation No 541/95 has no relevance whatsoever to the application of Article 4.8(a)(iii) of Directive 65/65, as amended.

59 The answer to the fourth question must therefore be that the fact that the original or abridged applications for marketing authorisations were made before the date on which Regulation No 541/95 entered into force does not affect the answers to the second and third questions.

The fifth question

60 The fifth question seeks to ascertain whether Article 4.8(a)(iii) of Directive 65/65, as amended, is invalid on the ground that it infringes the principles of protection of innovation, non-discrimination, proportionality, or respect for the right to property.

Infringement of the principle of non-discrimination

61 The Court has consistently held that the general principle of equality, which is one of the fundamental principles of Community law, requires that similar situations not be treated differently unless differentiation is objectively justified (see, *inter alia*, Joined Cases C-248/95 and C-249/95 *SAM Schiffahrt and Stapf* v *Germany* [1997] ECR I-4475, paragraph 50).

62 Glaxo and Wellcome submit in essence that if Article 4.8(a)(iii) of Directive 65/65, as amended, were to be interpreted in the manner advocated by the United Kingdom authorities, Generics or the Commission, a second applicant for marketing authorisation would be given an unjustified advantage over the first applicant, since he would be able to refer to the results of the pharmacological and toxicological tests and clinical trials, the costs of which are borne by the first applicant.

63 This line of argument is based on the premiss that the first and second applicants are in comparable situations. However, as the Commission has pointed out, the first applicant can show the efficacy and safety of the product only by means of the necessary tests. On the other hand, where the second applicant shows that his product is essentially similar to that of the first applicant, a product which has

already been authorised, he may refer to the data relating to the efficacy and safety of the original product which the first applicant has supplied without thereby creating a risk to public health.

64 It follows that the first and second applicants are not in comparable situations.

65 The argument based on infringement of the principle of non-discrimination must therefore be rejected.

Infringement of the principle of proportionality

66 According to the case-law of the Court, in order to establish whether a provision of Community law complies with the principle of proportionality it must be ascertained whether the means which it employs are suitable for the purpose of achieving the desired objective and whether they do not go beyond what is necessary to achieve it (see, in particular, Case C-127/95 *Norbrook Laboratories* v *MAFF* [1998] ECR I-1531, paragraph 89).

67 In a sphere in which the Community legislature is called on to undertake complex assessments, judicial review of the exercise of its powers must be limited to examining whether it is vitiated by a manifest error of assessment or a misuse of powers or whether the legislature has manifestly exceeded the limits of its discretion (see, to that effect, the judgment in *Norbrook Laboratories*, cited above, paragraph 90).

68 According to Squibb, Glaxo and Wellcome, the interpretation of Article 4.8(a)(iii) of Directive 65/65, as amended, advocated by the United Kingdom authorities, Generics or the Commission would make the provision disproportionate to the aim of the abridged procedure.

69 As the Court has already pointed out, in particular at paragraph 4 of this judgment, the purpose of the abridged procedure, and especially that provided for in the provision at issue, is to relieve applicants for marketing authorisation of the obligation to carry out pharmacological and toxicological tests and clinical trials.

70 Where it is clear that the medicinal product that is the subject-matter of an abridged application, within the meaning of the provision at issue, is essentially similar to a product which has been authorised within the Community and is marketed in the Member State for which the application is made, the results of pharmacological and toxicological tests and clinical trials covering all the therapeutic indications for which that product was authorised may be transposed to the medicinal product which is the subject-matter of that application. Consequently, repetition of those tests and trials is not necessary in order to protect public health, which, according to the first recital in the preamble to Directive 65/65, is the primary purpose of any rule concerning the production and distribution of medicinal products.

71 In fact, as stated in paragraph 4 of this judgment, one of the principal objectives of the abridged procedure is to avoid the repetition of tests on humans or animals unless absolutely necessary.

72 However, the second recital to Directive 87/21 intimates that it is necessary to state more precisely the cases in which the results of pharmacological and toxicological tests or clinical trials do not have to be provided with a view to obtaining authorisation for a medicinal product which is essentially similar to an authorised product, while ensuring that innovative firms are not placed at a disadvantage.

73 Safeguarding the interests of innovative firms is precisely the aim of granting them a period of protection for their data of 6 or 10 years from the date of the first marketing authorisation obtained in the Community for a particular product.

74 In the light of those considerations, the abridged procedure governed by the provision at issue, as interpreted in this judgment, is an appropriate and reasonable means of reconciling its aims.

75 In the present case Squibb, Glaxo and Wellcome have not shown that the Council infringed the principle of proportionality by adopting Article 4.8(a)(iii) of Directive 65/65, as amended, inasmuch as it provides that a medicinal product that is essentially similar to a product which has been authorised within the Community for not less than 6 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.

76 Consequently, the argument based on infringement of the principle of proportionality must be rejected.

Infringement of the principles of protection of innovation and of respect for the right to property

77 Glaxo, Wellcome and Squibb submit that Article 4.8(a)(iii), as interpreted by the United Kingdom authorities, Generics and the Commission, directly conflicts with the principle of the protection of innovation.

78 Since the alleged infringement of the principle of protection of innovation coincides, in the present context, with the alleged infringement of the principle of respect for the right to property, those two questions should be examined together.

79 Under the Court's case-law, the right to property forms part of the general principles of Community law. Those principles are not absolute, however, but must be viewed in relation to their social purpose. Consequently, the exercise of the right to property may be restricted, provided that the restrictions in fact correspond to objectives of general interest pursued by the Community and do not constitute disproportionate and unacceptable interference, impairing the very substance of the right guaranteed (see, in particular, the judgment in *SAM Schiffahrt and Stapf* v *Germany*, cited above, and Case C-200/96 *Metronome Musik* [1998] ECR I-1953, paragraph 21).

80 Glaxo, Wellcome and Squibb argue essentially that the provision in question disregards the principle of respect for the right to property inasmuch as it allows a second applicant to use, prior to the expiry of 6 or 10 years following their supply, data supplied by the first applicant in support of an application to extend the marketing authorisation of the original product.

81 As regards an original authorised medicinal product, it follows in particular from the reasoning set out in answer to the first two questions that Article 4.8(a)(iii) of Directive 65/65, as amended, must be interpreted as meaning that it confers on the owner of that product an exclusive right to make use of the results of the pharmacological and toxicological tests and clinical trials placed in the file on that product for a period of 6 or 10 years from the grant of the first marketing authorisation for that product in the Community.

82 Under that scheme, the actual duration of the right to exclusive use of the documentation making up the file depends, first, on the date of the grant of the first marketing authorisation for the original product and, second, the date on which

each document was lodged. It follows that such a document may, at most, receive protection for 6 or 10 years, but it may also, in certain cases, receive no protection.

83 As is apparent from the reasoning set out with regard to the plea of infringement of the principle of proportionality, the Community legislature took account of the interests of innovating firms in its approach to the right to property relating to pharmacological, toxicological and clinical data and, to a certain extent, ensured the protection of innovation, while pursuing the aim of avoiding repetition of tests on humans or animals unless absolutely necessary.

84 The Court therefore finds that the provision at issue is in accordance with objectives of general public importance pursued by the Community.

85 Nor can the provision at issue be regarded as disproportionate and unacceptable interference impairing the very substance of the right to property, since it does not appear that it is thereby rendered practically impossible for innovating firms to carry on their business of producing and developing medicinal products.

86 Consequently, the argument alleging infringement of the right to property must be rejected.

87 The answer to the national court must therefore be that consideration of the fifth question has not disclosed any factor of such a nature as to affect the validity of Article 4.8(a)(iii) of Directive 65/65, as amended.

Costs

88 The costs incurred by the United Kingdom, Danish, French, Swedish and Norwegian Governments and by the Council and 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 proceedings pending before the national court, the decision on costs is a matter for that court.

On those grounds,

THE COURT (Fifth Chamber),

in answer to the questions referred to it by the High Court of Justice (England & Wales), Queen's Bench Division, by order of 10 October 1996, hereby rules:

1. Article 4.8(a)(iii) of 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 87/21/EEC of 22 December 1986, must be interpreted as meaning that a medicinal product is essentially similar 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. The competent authority of a Member State may not disregard the three criteria set out above when it is required to determine whether a particular medicinal product is essentially similar to an original medicinal product.

2. A medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years and is marketed in the Member State for which the application is made may be authorised, under the abridged procedure provided for in Article 4.8(a)(iii) of Directive 65/65, as amended, for all therapeutic indications already authorised for that product.

3. A medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made may be authorised under the abridged procedure provided for in Article 4.8(a)(iii) of Directive 65/65, as amended, for all dosage forms, doses and dosage schedules already authorised for that product.

4. The fact that the original or abridged applications for marketing authorisations were made before entry into force of Commission Regulation (EC) No 541/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation granted by a competent authority of a Member State does not affect the answers to the second and third questions.

5. Consideration of the fifth question has not disclosed any factor of such a nature as to affect the validity of Article 4.8(a)(iii) of Directive 65/65, as amended.

Puissochet Moitinho de Almeida Gulmann

Sevón Wathelet

Delivered in open court in Luxembourg on 3 December 1998.

R. Grass J.-P. Puissochet

Registrar President of the Fifth Chamber