OPINION OF ADVOCATE GENERAL RUIZ-JARABO COLOMER
delivered on 22 January 1998 *

1. By order of 10 October 1996, received at the Registry of the Court of Justice on 22 November 1996, the High Court of Justice, Queen's Bench Division (hereinafter 'the High Court'), sought a preliminary ruling on a number of questions concerning the interpretation and validity of point 8(a)(iii) of the second paragraph of Article 4 of Council Directive 65/65/EEC, [1] as amended by Council Directive 87/21/EEC of 22 December 1986. [2]

2. Those questions relate to use of the simplified procedure for obtaining a marketing authorisation for generic medicinal products by reference to documentation which the innovating pharmaceutical undertaking produced in order to obtain authorisation for the original medicinal product. The specific issue here is whether the authorisation for the general medicinal product should extend to all the indications and dosage schedules authorised for the original medicinal product up to that time or whether, on the contrary, the protection period of 10 years for the original medicinal product should also be applied to the indications and dosage schedules for that medicinal product authorised subsequently.

The Community legislation

3. Medicinal products [3] intended for human use have considerable repercussions on public health and it is therefore necessary for their marketing to be strictly controlled by the authorities. In order progressively to reduce obstacles to the free movement of medicinal products in the Community resulting from divergences between national systems of control, the Community institutions have adopted numerous rules to harmonise controls on the marketing of medicinal products.

* Original language: Spanish.

1 — Directive 65/65/EEC of the Council of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ English Special Edition 1965-1966, p. 20).

2 — Council Directive 87/21/EEC of 22 December 1986 amending Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ 1987 L 15, p. 36).

3 — I shall treat the terms 'medicinal product' and 'proprietary medicinal product' as equivalent, even though the scope of the first term is wider than that of the second. The first covers not only medicinal products produced industrially and, in particular, generic medicinal products (that is to say, medicinal products similar to existing products not already protected by patents) but also proprietary medicinal products (that is to say, medicinal products prepared and marketed under a special name and in special packaging). Since the adoption of Council Directive 89/341/EEC of 3 May 1989 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC (OJ 1989 L 142, p. 11) the term medicinal product has been substituted for proprietary medicinal product in all Community legislation concerning medicinal products for human use.

4. The principal mechanism for verifying whether a medicinal product conforms with the requirements associated with the protection of public health is the marketing authorisation. At present two types coexist, Community authorisations and national authorisations.

On 1 January 1995 rules entered into force under which it is possible to obtain Community marketing authorisations valid in all the Member States. Authorisations of this kind can be obtained by means of the centralised procedure governed by Regulation (EEC) No 2309/93, [4] which establishes a Community authorisation granted by the Commission on the basis of action by the European Agency for the Evaluation of Medicinal Products created by that regulation.

The scope of Community authorisations is limited since they are compulsory for technologically advanced medicinal products and optional for medicinal products which contain new active principles.

4 — 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).

5. Most medicinal products are marketed after the issue of a national authorisation by the competent authority in a Member State which is valid in that State. [5] The harmonisation of national rules on the grant of authorisations for medicinal products started with Directive 65/65 which, after various amendments, continues to be the cornerstone of the Community legislation on medicinal products.

Article 3 of Directive 65/65 provides that a medicinal product may be marketed in a Member State only after the competent authority in that State has authorised it in accordance with that directive.

Article 4 defines the information and documentation needed in order to obtain a marketing authorisation, the content of which was harmonised by Directive 75/318/EEC [6] and by Directive 75/319/EEC. [7] According to that article, a person applying for an authorisation for a proprietary medicinal product for human use may do so by recourse to two

5 — Mutual recognition of national marketing authorisations has been facilitated by Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products (OJ 1993 L 214, p. 22).

6 — Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (OJ 1975 L 147, p. 1).

7 — Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of the provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ 1975 L 147, p. 13).

kinds of procedure: a normal procedure and a simplified procedure. Under the normal procedure, in order to obtain the marketing authorisation the applicant must submit the results of a series of pharmacological and toxicological tests and clinical trials, whereas that requirement will not apply, subject to certain conditions, if the matter is processed under the simplified procedure. The latter procedure enables a second applicant to avoid the investment of time and money involved in compiling detailed clinical and pre-clinical data.

6. Directive 87/21 amended Article 4 of Directive 65/65 as regards use of the simplified procedure. The purpose of the amendment is, according to the second recital in the preamble to Directive 87/21, to stipulate more precisely the cases in which, for authorisation of a proprietary medicinal product essentially similar to an authorised product, the results of pharmacological and toxicological tests or clinical trials do not have to be provided, whilst at the same time ensuring that innovative firms are not placed at a disadvantage. The fourth recital to that directive states that there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause. In pursuance of those objectives, Article 4 of Directive 65/65 provides:

'In order to obtain an authorisation to place a proprietary 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 proprietary 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 proprietary medicinal product has consented to the pharmacological, toxicological or clinical references contained in the file on the original proprietary 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 proprietary medicinal product have a well-established medicinal use, with recognised efficacy and an acceptable level of safety;

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

7. That provision, introduced by Directive 87/21, came into effect on 1 July 1987. As

from that date, pharmaceutical undertakings may use the simplified procedure to obtain an authorisation enabling them to market a medicinal product in the three cases contemplated in point 8(a) of the second paragraph of Article 4. In the first case, consent must be procured from the innovating firm holding the authorisation for the original medicinal product, which the undertaking producing the essentially similar medicinal product will have much difficulty in obtaining. In the second case, a marketing authorisation may be obtained on the basis of detailed references to published scientific literature. That possibility was improperly used by the national authorities [8] and Directive 87/21 seeks to reestablish its exceptional nature.

The third case, which gave rise to the dispute in these proceedings, allows an undertaking, after a period of 6 or 10 years, to use the abridged procedure to obtain a marketing authorisation for a generic medicinal product essentially similar to a medicinal product covered by an authorisation issued to the innovating firm which developed it. There is no doubt that it is a very important provision since it constitutes the basic means for obtaining authorisations to market generic medicinal products under the advantageous simplified procedure.

8 — See Case C-440/93 *R* v *Licensing Authority of the Department of Health, ex parte Scotia Pharmaceuticals* [1995] ECR I-2851.

8. In order to protect the industrial and commercial property of innovating firms, point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 does not allow recourse to the simplified procedure and consequent use of the documentation produced by the innovating undertaking for a period of 6 or 10 years, as decided by each Member State. The United Kingdom imposed a period of 10 years as from the issue of the first marketing authorisation for the medicinal product in question in a Member State of the Community.

Background to the dispute

9. These proceedings derive from three connected cases pending before the High Court which are concerned with three different pharmaceutical products, namely Captopril, Aciclovir and Ranitidine. I shall refer to those cases as 'the Captopril proceedings', 'the Aciclovir proceedings' and 'the Ranitidine proceedings'.

10. The respondent in each of those cases is the Licensing Authority established by the Medicines Act 1968, which is responsible for adopting decisions concerning the marketing of proprietary medicinal products in the United Kingdom. Except where marketing authorisations are granted for the entire Community — which is not the case here — prior authorisation from the Licensing Authority is

required for the sale of any medicinal product in the United Kingdom. The Medicines Control Agency (hereinafter 'the MCA') is the executive authority which deals with applications for authorisations on behalf of the Licensing Authority.

11. The applicants in the three cases are pharmaceutical undertakings specialising in the sale of generic medicinal products or pharmaceutical companies oriented towards the sale of non-generic proprietary medicinal products protected by a trade mark, which are developed following very considerable investment in research.

12. The subject-matter of the three cases is similar: the dispute centres on the extension of the marketing authorisation, applied for by the undertakings dealing in generic products under the simplified procedure provided for in point 8(a) of the second paragraph of Article 4 of Directive 65/65.

I shall now set out in greater detail the subject-matter of each of the three cases, which were described by the High Court in the schedule to its order for reference.

The Captopril proceedings

13. Captopril is a medicinal product developed as a result of research carried out in the 1970s by Bristol-Myers Squibb (hereinafter 'BMS'), a major research-based pharmaceutical manufacturer. It is a compound in the group of medicinal products called angiotensin converting enzyme inhibitors (ACE inhibitors). By a variety of effects (principally vasodilation) such compounds have a beneficial effect on, *inter alia*, the cardiovascular system. Captopril was the first of such class of compounds to be presented as a medicinal product and to receive a marketing authorisation within the Community.

14. On 27 March 1981 Squibb & Sons Limited (hereinafter 'Squibb'), the British subsidiary of BMS, was granted a marketing authorisation for a proprietary medicinal product under the brand-name 'Capoten' in the United Kingdom, the active ingredient of which was Captopril. Initially, the indication was for the treatment of severe hypertension where the usual therapy using diuretics proved unsuccessful. The product was marketed in the form of 25 mg, 50 mg and 100 mg tablets. After 1981, BMS continued research into other applications for Captopril in relation to conditions other than severe hypertension, and in other dosages. On the basis of the results obtained, the MCA approved a number of

changes to the United Kingdom marketing authorisation for Capoten. [9]

15. France was the first Member State to grant authorisation for the post-myocardial infarction indication, on 1 June 1993. The United Kingdom was the first Member State to grant authorisation for the diabetic nephropathy indication, on 5 May 1994. Substantial clinical research involving thousands of patients was conducted or sponsored by BMS to support each of the post-myocardial infarction and diabetic nephropathy indications. In both cases the costs of developing such research data and obtaining the authorisations exceeded several tens of millions of US dollars. All the other variations referred to above have been the subject of authorisation in other Member States for at least 10 years. Only the last two changes of indication and the status of the data underlying them are at issue in the Captopril proceedings.

16. On 20 January 1993 Generics (UK) Limited (hereinafter 'Generics') [10] applied for a marketing authorisation in respect of Captopril tablets of 12.5 mg, 25 mg and 50 mg. That application was made under point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65.

In response, the MCA informed Generics that it could not give a decision on its application without first analysing the provision relied upon and determining its proper interpretation. Generics commenced proceedings for judicial review, which were compromised on 18 July 1995 on the basis of an agreement between the parties, without prejudice to Generics's right to seek further judicial review. The MCA agreed to grant Generics marketing authorisation for Captopril tablets of 12.5 mg, 25 mg and 50 mg for indications which had been approved in the territory of the Community for 10 years. However, it declined to grant authorisations for all the other indications for Captopril which had not been approved in the territory of the Community for 10 years, namely treatment following myocardial infarction and diabetic nephropathy.

17. On 29 September 1995 Generics lodged a second application for judicial review of the MCA's decision refusing to grant marketing

9 — The changes were as follows:
- New indication for severe treatment-refractory congestive heart failure (6 October 1981).
- The introduction of a new 12.5 mg tablet (12 January 1983).
- New indication added for treatment for mild to moderate hypertension as an adjunct to thiazide therapy in patients who have not responded to thiazide treatment alone (23 October 1985).
- Indication varied to allow treatment for all congestive heart failure (13 June 1989).
- Indication varied to allow first-line treatment of mild to moderate hypertension (1 June 1990).
- New indication added relating to treatment of post-myocardial infarction (23 December 1993).
- New indication added in relation to treatment of diabetic nephropathy (5 May 1994).

10 — Generics is the United Kingdom operating subsidiary of the Generics Group of pharmaceutical companies. The Generic Group has affiliates in most Member States of the European Union and is 63.25% owned by the Dutch holding company Merck Generics BV. Generics carries on business in the United Kingdom as a manufacturer and distributor of 'generic' pharmaceuticals, that is to say drugs which are sold under their chemical name rather than, as with non-generic pharmaceuticals, a brand-name.

authorisations in respect of indications which had not been approved in the Community for 10 years.

18. On 23 October 1995 Generics received a letter [11] from the MCA dated 20 October 1995 which explained the MCA's interpretation of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65.

19. Subsequently, the MCA informed Generics that some of the Captopril indications added over the previous 10 years required a new authorisation under Annex II to Regulation (EC) No 541/95, [12] and therefore remained subject to protection. That was the case with regard to the additional indication for 'diabetic nephropathy'. However, the MCA accepted that Generics could rely upon point 8(a)(iii) of the second paragraph of Article 4 in respect of the indication for 'myocardial infarction' (an indication that had also been added within the previous 10 years), for which reason no new application under Annex II to Regulation No 541/95 would be required.

The Aciclovir proceedings

20. Wellcome Foundation Limited (hereinafter 'Wellcome') [13] holds the main authorisations for marketing in the United Kingdom of the anti-viral product Aciclovir, also marketed under the brand name 'Zovirax'. Those authorisations were granted to Wellcome by the MCA between 1981 and 1994.

21. During that period, Wellcome generated and filed new data in order to extend the permitted therapeutic indications to cover new forms and routes of administration for the product. Wellcome's development and

11 — The text of that letter was as follows:
'As you are aware, there has been considerable debate on the interpretation of Article 4.8(a)(iii) of Directive 65/65/EEC in relation to the exclusivity of data provided in respect of the originator's pharmaceutical and toxicological tests and clinical trial results.
After careful examination, the MCA has concluded that the Commission Regulation (EC) 541/95 Annex II concerning the examination of variations to the terms of a marketing authorisation can provide a transparent way forward in identifying the circumstances in which data supporting amendments to existing authorisations would be granted exclusivity.
It has been decided that, where the originator has added a new indication (during the last ten years) such that a new application would now be required under Commission Regulation (EC) 541/95 Annex II, and that change has been the subject either of a new marketing authorisation or has been "rolled back" into the original marketing authorisation, then ten years protection of new data submitted in support of the change would be given. It therefore follows that second Applicants may refer to the originator's data using Article 4.8(a)(iii) in respect of changes which do not meet the criteria in Annex II of 541/95. ...'

12 — 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).

13 — Wellcome is a major research-based United Kingdom pharmaceutical company. It is now a subsidiary of Glaxo Wellcome plc, which was formed in 1995 when Glaxo plc (formerly Glaxo Holdings plc) acquired Wellcome plc. Glaxo Wellcome plc is the largest pharmaceutical company in the world, with the largest share of the world market for prescription medicines and one of the largest, if not the largest, research and development programmes for medicinal products.

research expenditure amounted to several million pounds per annum; from UKL 4 million in 1982/1983 to UKL 8 million in 1991/1992. Over that period, Wellcome extended considerably the indications and dosages for Aciclovir. [14]

14 — The progressive extension of the authorised therapeutic indications and dosages may be summarised in two tables, one for aciclovir tablets and the other for aciclovir intravenous infusion.

Aciclovir Tablet Authorisation				
Date of UK authorisation or variation	Date of first EC authorisation or variation	Country of first EC authorisation or variation	Product	UK Indication/Nature of Variation (+)
27.01.83	27.01.83	UK	Zovirax Tablets 200 mg	Treatment of *Herpes simplex* virus infections of the skin and mucous membranes including initial and recurrent genital herpes
19.03.84	19.03.84	UK	Zovirax Tablets 200 mg	+ Profylaxis of *Herpes simplex* immune-compromised patients
08.10.86	26.06.86	Ireland	Zovirax Tablets 200 mg	+ Treatment of *Herpes zoster* (shingles) infections. + Suppression (prevention of recurrences) of *Herpes simplex* infections, in immunocompetent patients.
12.11.86	26.09.86	Ireland	Zovirax Tablets 400 mg	1. Treatment of *Herpes simplex* virus infections of the skin and mucous membranes including initial and recurrent genital herpes. 2. Suppression (prevention of recurrences) of recurrent *Herpes simplex* infections, in immuno-competent patients. 3. Profylaxis of *Herpes simplex* in immune-compromised patients. 4. Treatment of *Herpes zoster* (shingles) infections.
13.09.88	11.07.88	Holland	Zovirax Tablets 800 mg	Treatment of *Herpes zoster* (shingles) infections.
19.07.93	06.11.91	Spain	Zovirax Tablets 200 mg Zovirax Tablets 400 mg	+ Treatment of *varicela* (chickenpox) infections
26.07.94	06.11.91	Spain	Zovirax Tablets 800 mg	+ Treatment of *varicela* (Chickenpox) infections
Aciclovir Intravenous Infusion Authorisation				
06.04.82	06.04.82	UK	Zovirax I. V. 250 mg	Treatment of infections caused by *Herpes simplex* virus in immunocompromised patients, by the intravenous route.
09.11.83	09.11.83	UK	Zovirax I. V. 250 mg	+ Profylaxis of *Herpes simplex* infections in severely immunocompromised patients + Treatment of severe initial *Varicella zoster* (shingles) infections in patients with normal immune responses; primary and recurrent *Varicella zoster* in immunocompromised patients
09.04.86	09.04.86	UK	Zovirax I. V. 250 mg	+ Treatment of *Herpes encephalitis*
24.11.89	24.11.89	UK	Zovirax I. V. 250 mg Zovirax I. V. 500 mg	+ 500 mg Presentation
04.08.92	16.10.87	France	Zovirax I. V. 250 mg Zovirax I. V. 500 mg	+ Treatment of *Herpes simplex* infections in the neonate and infant up to 3 months of age

22. The number of tests and trials required for a new indication, route of administration or dosage form is not necessarily in proportion to the apparent size of the change. For example, to extend the indications of the 200 mg and 400 mg Aciclovir tablets (and subsequently also the 800 mg tablet) to cover the treatment of varicella infections, data was filed including the results of five clinical trials involving 1 241 patients, at a direct cost of UKL 240 000. The total amount of the research and development expenditure directed to obtaining the authorisation for that new indication has been estimated by Wellcome as in excess of UKL 6 million.

The Ranitidine proceedings

23. Wellcome became aware of the details of five marketing authorisations granted by the MCA to A/S Gea Farmaceutisk Fabrik (hereinafter 'Gea') for different indications and dosage forms of Aciclovir tablets and intravenous infusion. Those authorisations had been published in *The London Gazette* on 31 May 1996 and were dated 29 February 1996. They had been granted for Aciclovir tablets of 200 mg, 400 mg and 800 mg and for intravenous infusions of 250 mg and 500 mg, and each authorisation included all the main therapeutic indications for which Wellcome had obtained authorisation in the United Kingdom up to that time.

24. On 26 July 1996 Wellcome lodged an application for judicial review of the MCA's decision to grant marketing authorisations under point 8 of the second paragraph of Article 4 of Directive 65/65 to second applicants without the prior consent of Wellcome in respect of therapeutic indications, routes of administration and dosage forms for Aciclovir tablets and Aciclovir intravenous infusion which had been approved in the Community in earlier authorisations granted less than 10 years previously on the basis of data submitted by Wellcome.

25. Between 1981 and 1995 the MCA granted to Glaxo Operations UK Limited, Glaxo Wellcome UK Limited (formerly Glaxo Pharmaceuticals UK Limited), Glaxo Research and Development Limited (formerly Glaxo Group Research Limited) and Glaxo Group Limited (hereinafter 'Glaxo'), which are all subsidiaries of Glaxo Wellcome plc, various marketing authorisations for the anti-ulcer drug Ranitidine, also marketed under the brand name 'Zantac'.

26. During that period, Glaxo filed new data in order to extend the initial clinical indica-

tions and recommended dosing schedules. [15] Glaxo's research and development costs for Ranitidine amounted to several million pounds per year. For example, in order to extend the indications for Ranitidine tablets to cover the treatment of duodenal ulcers, the results of clinical trials involving over 2 200 patients were filed at a total estimated direct expense of UKL 1.326 million.

27. On 31 July 1992 Generics applied for a marketing authorisation for Ranitidine tablets of 150 mg and 300 mg, relying on point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65. In response, the MCA informed Generics that it could not give a decision on its application without first analysing the provision relied upon and determining its proper interpretation.

28. Generics commenced proceedings for judicial review (the same as for Captopril), which were compromised by an agreement with the MCA in terms similar to those relating to Captopril.

By letter of 7 April 1995, the respondent listed the indications for Ranitidine for which marketing authorisations were to be granted, as follows:

'The treatment of duodenal ulcer, benign gastric ulcer, post-operative ulcer, reflux

15 — The relevant authorisations previously granted to Glaxo for marketing Ranitidine in the United Kingdom are as follows:

Date of UK authorisation or variation of Zantac tablets	Date of first EC authorisation or variation	Country of first EC authorisation or variation	General nature of authorisation or variation in UK
10.06.87	10.06.87	UK	Treatment of chronic episodic dyspepsia
30.10.87	30.10.87	UK	300 mg od in the management of reflux oesophagitis
23.05.89	23.05.89	UK	Treatment of duodenal and benign gastric ulcers associated with NSAID [non steroidal anti-inflammatory drug] therapy
12.02.90	28.07.89	Italy	300 mg bd for duodenal ulcer
12.02.90	12.02.90	UK	300 mg qds for treatment of severe oesophagitis
19.07.91	08.05.91	Denmark	Prevention of duodenal ulcers associated with NSAID therapy
05.03.92	05.03.92	UK	150 mg qds for moderate/severe oesophagitis
05.03.92	05.03.92	UK	Increase of paediatric does for peptic ulcers
08.09.93	12.11.92	Italy	Long term management of healed oesophagitis
25.10.94	25.10.94	UK	Treatment of duodenal ulcers associated with *Heliobacter pylori*
06.11.95	10.02.94	Spain	Symptomatic relief of gastro-oesophageal reflux disease (GORD)

oesophagitis, the Zollinger-Ellison syndrome and the following conditions where reduction of gastric secretion and acid output is desirable: the prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients, the prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers and before general anaesthesia in patients considered to be a risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.'

Those indications corresponded to those appearing in the United Kingdom registration for Ranitidine from 1984/1985 to 1988/1989.

29. On 29 September 1995 Generics lodged a second application for judicial review (the same as for Captopril) of the MCA's decision refusing to grant it marketing authorisations for indications which had not been approved in the Community for 10 years.

The MCA confirmed to Generics that the position expressed in its letter of 20 October 1995 meant that all the Generics Ranitidine applications could now be processed under point 8(a)(iii) of the second paragraph of Article 4. As a result, Generics amended its application for judicial review, removing all references to Ranitidine.

30. On 16 August 1996 Glaxo commenced proceedings for judicial review of the MCA's decision which, under point 8 of the second paragraph of Article 4 of Directive 65/65, granted authorisations to second applicants, without Glaxo's consent for marketing, in respect of recommended clinical indications and recommended dosage schedules for Ranitidine tablets which had been approved in the Community in earlier authorisations granted less than 10 years previously on the basis of data submitted by Glaxo.

31. In order to determine the three sets of proceedings pending before it concerning Captopril, Aciclovir and Ranitidine, the High Court considered it necessary to seek a preliminary ruling from the Court of Justice on the following five questions:

' (1) (a) What is meant by "essentially similar" for the purposes of point 8(a)(iii) of the second paragraph of Article 4 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 amedicinal 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 point 8(a)(iii) of the second paragraph of Article 4 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 Community 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 point 8(a)(iii) of the second paragraph of Article 4 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 Community 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 point 8(a)(iii) of the second paragraph of Article 4 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

32. By its first question, the High Court asks the Court of Justice to specify which criteria are decisive in determining when two medicinal products are essentially similar, for the purposes of applying point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65, and to state whether the national authorities empowered to grant marketing authorisations have a margin of discretion in making that assessment.

33. Glaxo and Wellcome argue that a medicinal product is essentially similar to another authorised in the Community for 10 years only if all the characteristics of both, including their therapeutic indications and dosage schedules, are either identical or so closely similar that the results of the earlier pharmacological and toxicological tests and clinical trials can be regarded as equally applicable to both. Squibb considers that one product is essentially similar to another where both have characteristics, as defined in Article 4a of Directive 65/65, which are such as to enable the competent national authority to grant the marketing authorisation for the generic product by extrapolation from data submitted when an authorisation was sought for the original medicinal product.

34. Generics, the Commission and the French, Danish and United Kingdom Governments consider that two medicinal products are essentially similar where they have the same qualitative and quantitative composition in terms of active principles, they are in the same pharmaceutical form, and, where necessary, their bioequivalence has been demonstrated by appropriate bioavailability studies.

35. The latter interpretation of the term 'essentially similar' is the one which I consider to be appropriate, for the reasons which I set out below.

36. Directive 65/65 does not specify what the term 'essentially similar medicinal products' means. However, reference may usefully be made in interpreting that term to the minutes of the meeting of the Council of December 1986, which adopted Directive 87/21, in which the following definition of the term 'essentially similar' appears:

'The [two products have the] same qualitative and quantitative composition in terms of active principles, and the pharmaceutical form is the same, and where necessary bioequivalence with the first product has been demonstrated by appropriate bioavailability studies.'

37. I consider that those Council minutes contain an appropriate enumeration of the criteria which may be used to determine essential similarity as between two medicinal products. Those criteria are as follows:

— Qualitative and quantitative composition in terms of active principles. That composition is clearly described in the Annex to Directive 75/318, as amended by Directive 91/507/EEC. [16] Essential similarity as between two medicinal products depends only on their active principles and neither the constituents of the excipient nor those of the external covering of the medicinal products are relevant.

— The pharmaceutical form, which is defined in the standard terms drawn up by the Council of Europe under the auspices of the European Pharmacopaeia as follows: 'The *pharmaceutical form* is the combination of the form in which a pharmaceutical product is presented by manufacturer (*form of presentation*) and the form in which it is administered including the physical form (*form of administration*)'. [17] A medicinal product is essentially similar to another if both have the same form of presentation (tablet, drops to be taken orally in solution, injections, and so on) and the same form of administration (oral, rectal, nasal, cutaneous, and so on).

— Bioequivalence between the two medicinal products, demonstrated where necessary by appropriate bioavailability studies. [18] Point E of part 4 of the Annex to Directive 75/318, as amended by Directive 91/507, states that an assessment of bioavailability is to be undertaken where necessary to demonstrate bioequivalence for the medicinal products referred to in point 8(i), (ii) and (iii) of the second paragraph of Article 4 of Directive 65/65/EEC. The bioequivalence test generally provides the best way of establishing therapeutic equivalence between two medicinal products having the same active principles and the same pharmaceutical form, since the excipients and form of preparation may have an impact on their therapeutic effects.

38. Those three criteria are the ones which must be used to verify whether a medicinal product is essentially similar to another which has been authorised in the Community and

16 — 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).

17 — *Standard Terms, PharmaEuropa*, Special Edition, October 1996.

18 — The notice to applicants for marketing authorisations for medicinal products for human use in the Member States of the European Community, contained in Volume II of the *Guidelines on the quality, safety and efficacy of medicinal products for human use in the Member States of the European Community*, 1996 version, pp. 505 and 506, contains definitions of bioavailability and bioequivalence. Bioavailability means 'the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action. In the majority of cases substances are intended to exhibit a systematic therapeutic effect, and more practical definition can then be given, taking into consideration that the substance in the general circulation is in exchange with the substance at the site of action: bioavailability is understood to be the rate and extent to which a substance or its therapeutic moiety is delivered from a pharmaceutical form into the general circulation'. As regards bioequivalence, that document states as follows: 'Two medicinal products are bioequivalents if they are pharmaceutical equivalents or alternatives and if their bioavailability (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'.

whether, accordingly, a marketing authorisation may be obtained under the simplified procedure. The fact that indications, routes of administration and dosage schedules for two medicinal products coincide is not relevant in determining whether they are essentially similar, because such coincidence would make the medicinal products identical and would preclude recourse to the simplified procedure for a marketing authorisation for generic medicinal products whenever the innovative medicinal product underwent changes, albeit of inconsiderable extent, as regards its indications, routes of administration and dosage schedules.

39. Recourse to indications and dosage schedules as a criterion for determining essential similarity between two medicinal products finds no support in either Article 1 or Article 4a of Directive 65/65.

Article 1(2) defines medicinal products as follows:

'Any substance or combination of substances presented for treating or preventing disease in human beings or animals.

Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.'

The case-law of the Court of Justice has made it clear that the 'presentation' criterion used in the first subparagraph of that provision is designed to catch not only medicinal products having a genuine therapeutic or medical effect but also those that are not sufficiently effective or which do not produce the effect which their presentation might lead one to expect. [19] It may therefore be inferred that the word 'presented' cannot be regarded as including indications as a component of the definition of medicinal products.

Article 4a of Directive 65/65, inserted by Directive 83/570/EEC, [20] gives a summary of the characteristics of medicinal products, which includes, *inter alia*, therapeutic indications, methods of administration and dosage schedules. The inclusion of those data in the summary of characteristics of the medicinal product does not mean that those elements must be taken into account in determining essential similarity between two medicinal products, because the purpose of that sum-

19 — See Case C-112/89 *Upjohn* [1991] ECR I-1703, paragraph 16, and Case 227/82 *Van Bennekom* [1983] ECR 3883, paragraph 17.

20 — Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ 1983 L 332, p. 1).

mary is to give useful information concerning a medicinal product, once it has been defined, to the competent authorities of the Member States. In no case does the summary form part of the definition of the medicinal product.

40. Having regard to the foregoing considerations, I am of the opinion that two medicinal products are essentially similar where they have the same qualitative and quantitative composition in terms of active principles, their pharmaceutical form is the same and, where necessary, their bioequivalence has been demonstrated by means of appropriate bioavailability studies.

The use of those three objective criteria to determine essential similarity between two medicinal products for the purposes of applying point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 enables the simplified procedure for the grant of marketing authorisations for generic medicinal products to be applied uniformly throughout the Community.

Moreover, those criteria limit the margin of discretion available to the competent authorities of the Member States when determining whether two medicinal products are essentially similar in order to grant an authorisation for a generic medicinal product, on the basis of documentation submitted earlier for a marketing authorisation for the original medicinal product. In the same sense, it is clearly to be inferred from the case-law of the Court of Justice [21] that the national authorities do not enjoy a margin of discretion in applying the exceptions in point 8(a) of the second paragraph of Article 4 of Directive 65/65, which enable authorisations to be issued for medicinal products under the simplified procedure.

To allow the competent authorities of the Member States a margin of discretion in determining essential similarity between two medicinal products would also make it more difficult to apply the procedure for mutual recognition of marketing authorisations granted by Member States, established by Directive 93/39.

The second, third and fourth questions

41. By its second, third and fourth preliminary questions, the High Court asks the Court of Justice to determine the extent to which a marketing authorisation may be granted for a generic medical product which is essentially similar to an original medicinal product autho-

21 — *Scotia Pharmaceuticals*, cited above, paragraph 24, and Case C-210/94 *Smith & Nephew and Primecrown* [1996] ECR I-5819, paragraph 30.

rised in the Community or a Member State for at least 10 years.

In the questions submitted, the High Court sets out in part the views of the innovating pharmaceutical undertakings, the producers of generic medicinal products and the MCA.

The undertakings specialising in the production of innovative medicinal products consider that a marketing authorisation for a generic medical product essentially similar to an original medicinal product authorised in the Community or in a Member State should extend only to the therapeutic indications, routes of administration and dosage schedules which have been authorised for at least 10 years. In their opinion, the period of protection of 10 years must apply also to all new indications for the original medicinal product which were introduced after the issue of the marketing authorisation for it and for which the said protection period has not expired.

The undertakings producing generic medicinal products consider that the marketing authorisation for those medicinal products extends to all indications, routes of administration and dosage schedules authorised for the essentially similar original medicinal product up to the very moment when authorisation is applied for in respect of the generic medicinal product. In their view, the period of 10 years should not protect each of the subsequent modifications authorised for the original medicinal product.

The MCA adopts an intermediate position, taking the view that the marketing authorisation for the generic medicinal product will extend to all therapeutic indications authorised for the essentially similar original medicinal product, both the initial indications and those introduced subsequently for which the 10-year period has not expired, except where those modifications constitute an innovation of considerable therapeutic importance. In its view, an innovation displays such importance where it requires a fresh application for a marketing authorisation under Annex II to Regulation No 541/95.

42. Directive 65/65, as amended by Directive 87/21, provides no direct and clear answer to the questions submitted by the High Court, a fact which accounts for the differing interpretations referred to above. The interpretation to be adopted of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 will, however, have extremely far-reaching economic repercussions on the marketing of medicinal products in the Community and the development of the pharmaceutical industry as a whole.

43. Both those factors, it seems to me, make it necessary to undertake a detailed analysis of the various objectives pursued by Directive 65/65, as amended by Directive 87/21, [22] in order to arrive at an interpretation of point 8 of the second paragraph of Article 4 which strikes the best possible balance between those objectives.

The objectives of point 8 of the second paragraph of Article 4 of Directive 65/65

44. Point 8(a)(iii) of the second paragraph of Article 4, inserted in Directive 65/65 by Directive 87/21, introduced a third way of obtaining a marketing authorisation for generic medicinal products, under the simplified procedure, which makes it unnecessary to incur the research costs involved in filing the results of pharmacological and toxicological tests and clinical trials, since those tests and trials were described previously in connection with the marketing authorisation for an essentially similar original medicinal product. This form of application has become the one most used to obtain marketing authorisations for generic medicinal products, since the other two possibilities (consent from the undertaking holding the marketing authorisation for the original medicinal product and reference to scientific literature) involve greater difficulties.

45. When point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 is applied, the following essential interests must basically be taken into account:

(a) Protection of public health

46. The essential purpose pursued by Directive 65/65 and all the subsequent measures amending and implementing it is to safeguard public health. [23] That purpose is achieved principally by the control mechanism of the authorisations which must be issued by the competent national authorities before any medicinal product is marketed. Thus, the first recital in the preamble to Directive 87/21 states:

'... point 8 of the second paragraph of Article 4 of Council Directive 65/65/EEC, as last amended by Directive 83/570/EEC, provides that various types of proof of the safety and efficacy of a proprietary medicinal product may be put forward in an application for

22 — See the Opinion of Advocate General Léger in *Scotia Pharmaceuticals*, cited above, point 9 et seq.

23 — First recital in the preamble to Directive 65/65.

marketing authorisation depending upon the objective situation of the proprietary medicinal product in question'.

47. The case-law of the Court of Justice [24] has made it clear that the simplified procedure for marketing authorisations provided for in point 8 of the second paragraph of Article 4 does not affect the objective of safeguarding public health since it merely shortens the period for preparing an application for authorisation without in any way relaxing the requirements of safety and efficacy which must be met by medicinal products.

48. The safeguarding of public health also accounts for the last part of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65, which requires the undertaking manufacturing the generic medicinal product to submit the results of pharmacological and toxicological tests and clinical trials when applying for a marketing authorisation for indications, routes of administration or dosage schedules different from those authorised for the essentially similar original medicinal product marketed for more than 6 or 10 years in the Community.

24 — *Scotia Pharmaceuticals*, cited above, paragraph 17.

49. Finally, I would point out that the protection of public health is compatible with an extension of the marketing authorisation for generic medicinal products so as to include all indications, routes of administration and dosage schedules authorised for the original medicinal product up to the time of issue of that authorisation.

(b) Protection of research and innovation in the pharmaceutical sphere

50. The importance of experience as a decisive criterion in the achievement of medicinal innovations was highlighted by many Renaissance researchers, [25] who emphasised the role played by the passage of time in relation to the discovery not only of new remedies but also of new therapeutic properties of existing remedies. The idea of progress is inseparable from scientific advances relating to health.

25 — N. Monardes, *La Historia medicinal de les cosas que se traen de nuestras Indias Occidentales (1565/1574)*, Ministerio de Sanidad y Consumo, Madrid, 1989, attaches importance in the introduction to his work to 'the many things that there are in diverse parts of the world which were unknown until the present time; they were unknown in ancient times, but time, which is the discoverer of all things, has shown them to us' (pp. 92 and 93). In the chapter devoted to 'sangre de drago', used to treat stomach disorders and to strengthen the gums, he refers to the 'thousand follies' spoken by 'the ancients, whether Greek, Roman or Arab', which have been rendered outmoded by what 'time, which is the discoverer of all things, has revealed to us and taught us' (pp. 218 and 219).

Innovative pharmaceutical undertakings make substantial investments in research and development to develop new medicinal products. Such innovation is essential to ensure the existence of a sound pharmaceutical industry in the Community. For that reason, it is stated in the second recital in the preamble to Directive 65/65 that Community harmonisation should not hinder the development of the pharmaceutical industry. Similarly, it is stated in the second recital to the preamble in Directive 87/21 that it is necessary to define more precisely the cases in which the simplified procedure may be used '... while ensuring that innovative firms are not placed at a disadvantage'.

51. In the Commission's *travaux preparatoires* [26] prior to the adoption of Directive 87/21 it is clearly stated that one of the objectives pursued is the protection of research and innovation in the pharmaceutical sphere. The Commission laid stress on the costs which had to be borne by innovative undertakings to obtain the initial marketing authorisation for a medicinal product and stated that certain national authorities too easily allowed recourse to the simplified procedure, based on references to scientific literature, by undertakings producing generic medicinal products. According to the Commission, that practice was prejudicial to innovative undertakings holding marketing authorisations for original medicinal products.

52. The 6 or 10 year protection period of the marketing authorisation for original medicinal products is specifically intended to safeguard the interests of innovative undertakings and foster research in the pharmaceutical sector. Moreover, Directive 87/21 incorporates specifically in point 8 of the second paragraph of Article 4 of Directive 65/65 the principle that the simplified procedure will not be available where it might undermine rights under the law relating to the protection of industrial and commercial property.

53. Innovation in the pharmaceutical sphere is also safeguarded by other Community, national and international provisions relating to protection of intellectual property, in particular patents. [27]

Article 52(4) of the 1973 Munich Convention on the Grant of European Patents does not regard as patentable inventions those relating to methods for treatment of the human or animal body by surgery or therapy or diagnostic methods practised on the human or animal body. Nevertheless, Article 54(5) allows the patenting of substances for use in the preparation of medicinal products, and therefore the latter can benefit from the 20-year protection provided for in the convention. In the domestic laws of the Member States there has been a similar trend and they recognise

26 — COM(84) 437 final of 25 September 1984, paragraphs 14 and 15.

27 — See, in that connection, P. Leardini, 'Brevets', *Joly Communautaire*, Paris, December 1997.

the possibility of granting patents for medicinal products. [28]

In Community law, a supplementary protection certificate was introduced by Regulation (EEC) No 1768/92, [29] in order to compensate for the period extending from the filing of a patent application for a medicinal product to the grant of a marketing authorisation. [30]

54. In my opinion, in order to protect innovation and pharmaceutical research, it is advisable to apply the 6 or 10 year protection period to all new indications of considerable therapeutic importance authorised for an original medicinal product essentially similar to a generic medicinal product.

(c) Non-repetition of tests on persons or animals

55. The fourth recital in the preamble to Directive 87/21 states that 'there are reasons of public policy for not conducting repetitive tests on humans or animals without overriding cause'. The limitation of repetitive trials on persons or animals, whenever they are not strictly necessary, is a well-established rule in Community law, [31] which is logically mirrored by the simplified procedure for applying for marketing authorisations for generic medicinal products. If the innovative undertaking has carried out the relevant tests to obtain an authorisation for the original medicinal product, there is no need to repeat those same tests to obtain an authorisation for an essentially similar generic medicinal product.

56. As regards therapeutic indications, routes of administration and dosage schedules authorised for the original medicinal product for less than 6 or 10 years, the rule precluding the repetition of tests on persons or animals provides a basis for arguing that the marketing authorisation for the generic medicinal product should be extended as far as possible, so as to cover all indications, routes of administration and dosage schedules of the original medicinal product, even if authorised for less than 6 or 10 years.

28 — The present situation has been described by Advocate General Fennelly in his Opinion in Joined Cases C-267/95 and C-268/95 *Merck and Beecham* [1996] ECR I-6285, points 75 to 87.

29 — Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products (OJ 1992 L 182, p. 1).

30 — This regulation has been interpreted by the Court of Justice in, *inter alia*, Case C-350/92 *Spain* v *Council* [1995] ECR I-1985; Case C-181/95 *Biogen* [1997] ECR I-357, and Case C-110/95 *Yamanouchi Pharmaceutical* [1997] ECR I-3251.

31 — See Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (OJ 1986 L 358, p. 1).

Extension of the marketing authorisation for generic medicinal products

57. The different objectives which come together in the application of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 are difficult to reconcile because each of them justifies a different reading of that provision. Nevertheless, I consider that the best accommodation of the interests involved in recourse to the simplified procedure for obtaining marketing authorisations for generic medicinal products follows from the interpretation of that provision which I propose below.

Marketing authorisations for generic medicinal products, applied for under that provision, will cover all indications, routes of administration and dosage schedules authorised up to that time for the essentially similar original medicinal product marketed in the Community for 6 or 10 years. Nevertheless, new indications for the original medicinal product, which have been authorised for at least 6 or 10 years, will also enjoy the 6 or 10 year protection period where they constitute therapeutic innovations of considerable importance. New routes of administration and dosage schedules for the original medicinal product do not constitute significant therapeutic innovations and, consequently, are not covered by that protection period.

58. That interpretation of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65, which basically coincides with that contended for by the Commission, respects the requirement of protection of public health because the extension of a marketing authorisation for a generic medicinal product so as to cover new indications for the original medicinal product which are of scant therapeutic relevance and to cover new routes of administration and dosage schedules is based on the existence of the relevant results of the pharmacological and toxicological tests and clinical trials submitted by the innovative undertaking. Moreover, the documents and reports needed for an application for a marketing authorisation for a generic medicinal product will be prepared by experts having the necessary technical or professional qualifications, as required by Directives 75/318 and 75/319.

Furthermore, it is conducive to the protection of public health for a generic medicinal product to be marketed on the basis of reference to all the therapeutic indications, routes of administration and dosage schedules accepted by the competent authorities for the essentially similar original medicinal product. In that way the maximum therapeutic yield is obtained from generic medicinal products.

Finally, the proposed interpretation prevents innovative undertakings which obtain a marketing authorisation for an original medicinal product from resorting to an obstructive

strategy regarding essentially similar generic medicinal products. Such a strategy might consist in seeking, at intervals, authorisation for new therapeutic indications, routes of administration and/or dosage schedules in order to extend the 6 or 10 year protection period and hamper the bringing to market of generic medicinal products. Such practices would be incompatible with the free movement of medicinal products in the Community and would restrict freedom of competition in the pharmaceutical industry, without in any way enhancing the protection of public health.

When the undertaking holding the marketing authorisation for the original medicinal product obtains authorisations for new routes of administration or dosage schedules, it does not need to carry out significant research deserving of special protection because the innovation involved in those modifications is of little significance. The same reasoning applies to new therapeutic indications for the original medicinal product which fall into the same category as those authorised earlier.

59. The interpretation suggested is also in harmony with the rule requiring non-repetition of tests on persons and animals unless strictly necessary. New therapeutic indications, routes of administration and/or dosage schedules authorised for an original medicinal product are supported by the tests carried out by the innovative undertaking and it is not advisable that they be repeated merely because there has not been a time lapse of more than 6 or 10 years since the authorisation of those modifications.

In my opinion, there is a significant innovation only where the undertaking holding the marketing authorisation for the original medicinal product obtains a subsequent authorisation for a new indication of great therapeutic importance. In such a case, it is appropriate to apply the 6 or 10 year protection period to the new indication in order to protect the innovation achieved by the pharmaceutical undertaking, because it is thereby possible to amortise the substantial investments normally required to achieve a significant innovation. A new indication of considerable therapeutic importance will normally require new pharmacological and toxicological tests and clinical trials of a scope similar to those needed to obtain a marketing authorisation for any new medicinal product.

60. The encouragement of pharmaceutical innovation and research, and the protection of the industrial and commercial property of innovative undertakings, are also ensured to the proper extent by the interpretation which I propose of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65.

61. The application of that interpretation of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 calls for details of

the criteria which may be applied to determine which new indications for the original medicinal product constitute a therapeutic innovation of great significance deserving of additional protection.

62. For that purpose, the MCA relied upon Regulation No 541/95 as a basis for determining when a new therapeutic indication is of great importance. The Commission, Glaxo, Wellcome, Squibb, Generics and the Swedish and Danish Governments consider recourse to that regulation to be inappropriate.

In my opinion, it is not possible to derive from Regulation No 541/95 criteria by which to determine whether or not a new indication for an original medicinal product is of great therapeutic importance. That regulation is a measure of a procedural nature which supplements Articles 7 and 7a of Directive 65/65, which were amended by Directive 93/39, concerning procedures for mutual recognition of marketing authorisations for medicinal products issued by the competent authorities of the Member States. Regulation No 541/95 extends the provisions on mutual recognition to changes in the terms of marketing authorisations for medicinal products. That regulation distinguishes between minor variations and major variations. The latter, enumerated in Annex II to the regulation, involve a radical alteration of the terms of the marketing authorisation, which means that a new application for an authorisation must be submitted.

There is no basis for the view taken by the MCA that those major variations constitute new indications of great therapeutic importance which require additional protection by virtue of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65. In the first place, Annex II to Regulation No 541/95 states that 'This Annex is without prejudice to the provisions of Article 4 of Directive 65/65/EEC...'. Secondly, a therapeutic innovation is not a relevant factor for the purpose of classifying variations as being major or minor. Finally, that regulation is of a merely formal nature and does no more than harmonise administrative practices applicable to changes in the terms of marketing authorisations, which renders it inapplicable so far as concerns determining the substantive conditions to be met for the grant of authorisations for generic medicinal products under the abridged procedure.

63. In my opinion, it is for the national competent authorities to determine in each specific case whether a new indication for an original medicinal product authorised for less than 6 or 10 years constitutes a therapeutic innovation of great significance deserving supplementary protection in relation to an essentially similar generic medicinal product. In carrying out that assessment, the competent

authorities of the Member States must, as the Commission indicates, take account *inter alia* of the following criteria:

— The eligibility of the new indication for the issue of a Community marketing authorisation, by virtue of the third indent of part B of the Annex to Regulation No 2309/93, which requires that the significance of its therapeutic benefit be proved to the European Agency for the Evaluation of Medicinal Products.

— The possibility that the new therapeutic indication may be eligible for a patent [32] under the Munich Convention or the national legislation of a Member State. The initial therapeutic indications for an original medicinal product can be patented and it is also possible to patent subsequent therapeutic indications provided that they constitute a novelty deriving from inventive effort and are capable of being put to practical therapeutic use. The eligibility for patent protection of a new therapeutic indication for an original medicinal product is indicative of the therapeutic innovation embodied in it and for that reason is a factor to be taken into account in determining whether or not the new indication deserves additional protection in relation to the marketing of an essentially similar generic product.

— The scope of the pharmacological and the toxicological tests and clinical trials carried out by the innovative undertaking in order to discover the new therapeutic indication for the original medicinal product.

64. Those criteria enable the competent national authorities to carry out their assessment with a sufficient measure of objectivity.

The fifth question

65. This question raises the question of the possible invalidity of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 on the ground that it breaches the principles of protection of innovation, non-discrimination, proportionality and/or respect for property.

66. In its order for reference, the High Court does not indicate the reasons which prompted it to raise the possibility that the provision in question may be invalid as being incompatible with those general principles of Community law. Personally, I perceive nothing in

32 — The Court of Justice has considered the relationship between patents and marketing authorisations from another standpoint in Case C-316/95 *Generics* [1997] ECR I-3954.

point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 which might be contrary to any of those general principles.

67. Protection of innovation has not been formally recognised as a general principle of law by the case-law of the Court of Justice. It is a purpose pursued by the Community rules on the marketing of medicinal products which, as such, is mentioned in various Community measures. [33] On the other hand, the principles of non-discrimination [34] and proportionality [35] are enshrined in settled case-law of the Court of Justice.

Point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 provides for a simplified marketing authorisation procedure for generic medicinal products essentially similar to original medicinal products that have been marketed for 6 or 10 years, in which use is made of the results of the pharmacological and toxicological tests and clinical trials submitted by the innovative undertaking. That procedure is in conformity with the principle of proportionality since it is appropriate in order to ensure the protection of public health, non-repetition of tests on persons and animals, and protection of innovation and pharmaceutical research. [36] Moreover, it does not give rise to discrimination between innovative undertakings and those which produce generic medicinal products, since the former enjoy a protection period of 6 or 10 years for their innovations, enabling them to amortise their investments in research and development of medicinal products, and the latter are able to market generic medicinal products essentially similar to the original medicinal products following a simplified and less costly procedure which relies on the results of the research carried out by the innovative undertakings.

68. As regards respect for property, the Court of Justice has held that it is a right upheld in the Community legal order but one which may be subject to restrictions which correspond to objectives of general interest and do not constitute, having regard to the aim pursued, a disproportionate and intolerable interference impairing the very substance of the rights guaranteed. [37] The use, upon expiry of the protection period of 6 or 10 years, by undertakings producing generic medicinal products of the results of the pharmacological and toxicological tests and clinical trials submitted by the innovative undertakings in order

33 — See paragraphs 51 to 55 above.

34 — Case 203/86 *Spain* v *Council* [1988] ECR 4563, paragraph 14, and Case C-22/94 *Irish Farmers Association and Others* v *Minister for Agriculture, Food and Forestry, Ireland, and the Attorney General* [1997] ECR I-1809, paragraph 34.

35 — Joined Cases C-296/93 and C-307/93 *France and Ireland* v *Commission* [1996] ECR I-795, paragraph 30; Case C-280/93 *Germany* v *Council* [1994] ECR I-4973, paragraph 90, and Case C-331/88 *Fedesa and Others* [1990] ECR I-4023, paragraph 14.

36 — See points 45 to 56 above.

37 — Case 5/88 *Wachauf* [1989] ECR 2609, paragraph 18; Case C-177/90 *Kühn* [1992] ECR I-35, paragraph 16, and Case C-280/93 *Germany* v *Council* [1994] ECR I-4973, paragraph 78.

to obtain a marketing authorisation for the original medicinal product does not constitute a disproportionate interference impairing their property rights in respect of those results.

69. Consequently, I do not perceive any factor such as to affect the validity of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65.

Conclusion

70. In view of the foregoing considerations I propose that the Court of Justice answer the questions referred to it as follows:

(1) Two medicinal products are essentially similar where they have the same qualitative and quantitative composition in terms of active principals, their pharmaceutical form is identical and, where necessary, their bioequivalence has been demonstrated by means of appropriate bioavailability studies.

(2) The competent national authorities enjoy no margin of discretion in assessing essential similarity between two medicinal products for the purposes of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65 of the Council of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products.

(3) Marketing authorisations for generic medicinal products will extend to all indications, routes of administration and dosage schedules authorised until that time for the essentially similar original medicinal product which has been marketed in the Community for 6 or 10 years. Nevertheless, new therapeutic indications for the original medicinal product, authorised less than 6 or 10 years earlier, will enjoy protection for a period of 6 or 10 years where they constitute therapeutic innovations of great significance.

(4) 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 has no bearing on the application of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65.

(5) In this case, no factor has been disclosed of such a nature as to affect the validity of point 8(a)(iii) of the second paragraph of Article 4 of Directive 65/65.