OPINION OF ADVOCATE GENERAL JACOBS
delivered on 23 January 2003 [1]

1. In the present case the Court of Appeal of England and Wales (Civil Division) asks the Court six questions concerning the conditions which must be met under Community law before the competent authority in a Member State may authorise the marketing of a medicinal product in that Member State.

2. In particular, the proceedings raise three issues relating to Article 4 of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products ('the Directive'), [2] as amended by Council Directive 87/21/EEC of 22 December 1986. [3] They allow the Court to consider further the interpretation of that Article which it developed in the *Generics* case. [4] The first issue concerns the circumstances in which a national licensing authority, processing an application for the marketing authorisation of a medicinal product pursuant to point 8 (a)(iii) of the third paragraph [5] of Article 4 of the Directive ('point 8(a)(iii)'), may make use of data submitted to it by a different applicant in respect of another product authorised within the six or ten year period specified in that provision. The second issue is whether, in order to obtain authorisation of a new product in reliance on the proviso contained in the final subparagraph of point 8(a) ('the proviso') in conjunction with point 8(a)(i) of the third paragraph of Article 4 ('point 8(a)(i)') or point 8(a)(iii), it is necessary to demonstrate the essential similarity of the new product to the reference product specified pursuant to those latter provisions. The third issue relates to the circumstances in which one product can be said to be 'essentially similar' to another for the purposes of points 8(a)(i) and (iii).

1 — Original language: English.

2 — OJ, English Special Edition 1965-1966, p. 20.

3 — OJ 1987 L 15, p. 36.

4 — Case C-368/96 *Generics (UK) and Others* [1998] ECR I-7967.

5 — The paragraph in question was originally the second of Article 4, but became the third in consequence of an amendment effected by Article 1(2) of Council Directive 93/39/EEC of 14 June 1993, OJ 1993 L 214, p. 22.

Legal framework

3. Given the obvious need to regulate the marketing of medicinal products in the interests of public health, and in order to reduce obstacles to the free movement of such products within 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.

4. The primary method for verifying whether a medicinal product conforms with the requirements associated with the protection of public health is the marketing authorisation, of which there are two types: Community-wide authorisations [6] and national authorisations.

5. The present proceedings are concerned exclusively with the Community rules relating to national authorisations, which at the material time [7] were primarily contained in Chapter II of the Directive as amended, in particular, by Directive 87/21.

Article 3 of the Directive provides that, in the absence of a Community-wide authorisation, a medicinal product may be marketed in a Member State only after authorisation has been obtained from the competent authority in that Member State.

6. Article 4 defines in detail the procedure, documents and information needed in order to obtain a marketing authorisation from the competent authority of a Member State. In effect, it creates several possible procedural routes for obtaining a national marketing authorisation. Under the full procedure, an application for a marketing authorisation must, by point 8 of the third paragraph of that Article ('point 8'), be accompanied by the results of:

'— physico-chemical, biological or microbiological tests;

— pharmacological and toxicological tests;

— clinical trials.'

7. Point 8(a) of the third paragraph of Article 4 ('point 8(a)') provides for an alternative, abridged procedure, whereby,

6 — Community-wide authorisations are governed by Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medical products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, OJ 1993 L 214, p. 1.

7 — The Community legislative framework for medicinal products has with effect from 18 December 2001 been codified and consolidated in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ 2001 L 311, p. 67.

in certain specified circumstances, an applicant for a marketing authorisation may be relieved of the obligation to provide the results of pharmacological and toxicological tests and of clinical trials ordinarily required by point 8, and may rely instead on data submitted in respect of another 'reference' product which has already been authorised. The obligation to provide full particulars of the physico-chemical nature of the product is not affected. In order to avail itself of the 'abridged procedure' an applicant must demonstrate:

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

...

(iii) or that the medicinal product is essentially similar to a product which has been authorised within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made; ... a Member State may... 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 interests of public health ...'

8. The final subparagraph of point 8(a) contains the following proviso to the abridged procedure established by that provision:

'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 tests and/or of appropriate clinical trials must be provided.'

9. The proviso thus has the effect of establishing a further procedure for obtaining marketing authorisation, often termed and hereafter referred to as the hybrid abridged procedure.

10. Under that procedure, the applicant is required to provide only the results of such pharmacological and toxicological tests and clinical trials as are appropriate in the light of the difference in therapeutic use, route of application or dose from the other medic-

inal products marketed. Otherwise, the applicant relies upon the data relating to the reference product which it is required to specify under point 8(a)(i) or (iii).

11. The hybrid abridged procedure is therefore intermediate between the abridged and the normal procedure as regards the evidential burden which it imposes on the applicant. The fresh data which an applicant is required to submit pursuant to the hybrid abridged procedure are referred to as bridging data.

12. Guidance as to the nature of the tests and trials required in order to satisfy the various procedures laid down by Article 4 of the Directive is set out in the Annex to Council Directive 75/318 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 [8] as amended by Council Directive 91/507 of 19 July 1991.[9] The Annex to Directive 75/318 requires the particulars and documents accompanying an application for marketing approval to take account of the guidance published by the European Commission in 'The Rules governing Medicinal Products in the European Community', including volume 2 (known as the Notice to Applicants) and volume 3 (known as the Community Guidelines).

13. The 1993 version of the Notice to Applicants (volume 2A at paragraph 3.3) explained the hybrid abridged procedure in the following terms:

'After 6 or 10 years' knowledge and experience with a medicinal product, it would be inappropriate for ethical and scientific reasons to require a second applicant to repeat all tests, studies and trials, which are already known to the authorities. For a medicinal product which does not fall within the strict requirements of essential similarity, and therefore does not benefit from the exception from providing results of pharmacological, toxicological and clinical trials, [the proviso] requires results of appropriate pharmacological and toxicological tests and/or appropriate clinical trials.'

8 — OJ 1975 L 147, p. 1.
9 — OJ 1991 L 270, p. 32.

That passage has, however, been omitted from subsequent editions of the Notice to Applicants.

14. The purposes underlying Article 4 are apparent from the preambles to the Directive and to Directive 87/21, which introduced the abridged procedures in their current form. The first recital of the preamble to the Directive makes clear that the primary purpose underlying all the rules governing the marketing authorisation of medicinal products is the protection of public health. As appears from the second and fourth recitals of the preamble to Directive 87/21, point 8(a)(iii) is also aimed at ensuring that innovative firms are not placed at a disadvantage and at avoiding unnecessary medical testing on humans and animals.

15. Article 5 of the Directive provides that an application for a marketing authorisation must be refused 'if, after verification of the particulars and documents listed in Article 4, it proves that the medicinal product is harmful in the normal conditions of use or that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or that its qualitative or quantitative composition is not as declared'. Authorisation must likewise be refused if 'the particulars and documents submitted in support of the application do not comply with Article 4'.

16. 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 [10] provides that certain changes to a marketing authorisation, a list of which is set out in that Annex, are to be considered fundamentally to alter the terms of that authorisation and therefore to require an application to vary the terms of the marketing authorisation. The types of change identified in the Annex in respect of medicinal products for human use are changes to the active substance(s) of a product, changes to the therapeutic indications, and changes to dose, pharmaceutical form and route of administration.

17. In the United Kingdom, the licensing authority established by the Medicines Act 1968 is designated as the competent authority for the purposes of the Directive. It operates administratively through an executive agency of the Department of Health, the Medicines Control Agency ('the MCA'), and it is the MCA which processes applications for marketing authorisations on behalf of the licensing authority. Point 8 is implemented in the United Kingdom by the Medicines for Human Use (Marketing Authorisations etc.) Regulations 1994. By Regulation 4 (6), the United Kingdom has exercised its

10 — OJ 1995 L 55, p. 7.

option, pursuant to point 8(a)(iii), to extend the period specified in that provision from 6 to 10 years.

18. The Court of Justice was called upon to consider the interpretation of point 8(a)(iii) in the *Generics* case, [11] which arose out of a challenge brought by several pharmaceutical companies against the decisional practice of the MCA when considering applications for authorisation to market generic copies of existing medicinal products pursuant to that provision. The MCA had been granting authorisations not only for such indications, dosage schedules, doses or dosage forms as had been authorised in respect of the reference product for at least 10 years, but also for additions or changes authorised more recently. The MCA would only decline to authorise a generic product for such additions or changes if they were deemed to constitute major therapeutic innovations, such as would necessitate a new application for marketing authorisation under Annex II to Regulation No 541/95.

19. The High Court referred various questions as to when two products would be considered essentially similar under point 8 (a) and as to how extensive an authorisation a competent authority was entitled to grant following an application made under point 8(a)(iii).

20. As regards the meaning of essential similarity, the Court of Justice held that one medicinal product is essentially similar to another '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'.

21. As the Court explained, two products are regarded as being bioequivalent if they are pharmaceutical equivalents or alternatives and if their bioavailabilities (i.e. the rate and extent of their absorption into the body and transfer to the site of action) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same. [12]

22. As regards the extent of any authorisation granted under the abridged procedure provided for in point 8(a)(iii), the Court held that a medicinal product which 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 that

11 — Cited above in note 4.

12 — Paragraph 31 of the judgment.

provision for all therapeutic indications, dosage forms, doses and dosage schedules already authorised for the reference product, including those authorised for less than 6 or 10 years.

Facts

23. In the present case, Novartis Pharmaceuticals Ltd ('Novartis') challenges the validity of marketing authorisations granted by the MCA to SangStat UK Ltd, another pharmaceuticals company, and Imtix-SangStat UK Ltd, its distributor in the United Kingdom, in respect of two medicinal products, SangCya Oral Solution and Acceptine Oral Solution (for present purposes identical, and henceforward referred to collectively as SangCya).

24. SangCya competes on the market with two of Novartis' products, Sandimmun and Neoral. All three products are immunosuppressants, and contain the same active ingredient, cyclosporin, used to prevent rejection of organs or tissue in patients who have undergone transplant surgery, and in the treatment of various autoimmune diseases.

25. Each of the three products is administered orally, in the form of a solution. There are, however, differences between Novartis' first product, Sandimmun, its second product, Neoral, and SangStat's products, SangCya. When diluted for administration to the patient, they react differently. Whereas Sandimmun forms a macro-emulsion in an aqueous environment, Neoral forms a micro-emulsion, and SangCya undergoes a nano-dispersion process. As a consequence, the three products are not bioequivalent: they vary in their bioavailability, that is, the rate and extent of their absorption into the body and transfer to the site of action. This is significant because cyclosporin has a narrow therapeutic index. If the patient receives too much or too little of it, it will not be effective, and may be detrimental to health. As a consequence, the actual level of cyclosporin in the blood of a patient has to be monitored and the dosage adjusted as necessary.

26. Sandimmun was the first cyclosporin product to be authorised within the European Union. It was authorised in the United Kingdom in 1983 following submission by Sandoz Pharmaceuticals (UK) Ltd, now Novartis, of the complete dossier of information required under the full procedure.

27. Neoral was first authorised for marketing within the European Union in Germany in 1994. A United Kingdom marketing authorisation was granted in 1995, following what was apparently a hybrid abridged procedure, made pursuant to point 8(a)(i) in conjunction with the proviso, using Sandimmun as the reference product. The application therefore partly rested upon

data filed in respect of the Sandimmun application, consent having been given (by Novartis as the developer of Sandimmun to itself as the developer of Neoral), and partly on bridging data prepared specifically in relation to Neoral. During the application process, and following meetings between Novartis and the MCA at which the MCA indicated that authorisation would not be granted without the submission of long-term clinical trial data, Novartis extended its clinical trials so as to be able to provide more substantial bridging data. Neoral was approved for all of the same indications as Sandimmun, and in 1997 received approval for a further set of indications. Sandimmun remains on the market in the United Kingdom but represents only a small percentage of the total cyclosporin market as compared with Neoral.

28. The authorisations in respect of SangCya, which are at issue in the present proceedings, were also granted under the hybrid abridged procedure, pursuant to point 8(a)(iii) in conjunction with the proviso. The reference product identified by SangStat in its application was Sandimmun, which had been authorised more than 10 years previously.

29. The MCA granted marketing authorisations to SangCya in January 1999. It based its decisions on the essential similarity of SangCya to Sandimmun. However, it relied not only upon the data submitted by Novartis in respect of Sandimmun, but also upon the data which Novartis had supplied five years previously in respect of Neoral. It did not require SangStat to submit further and more extensive bridging data regarding SangCya equivalent to the data which Novartis had been required to submit regarding Neoral.

National proceedings and questions referred

30. Novartis has brought proceedings for judicial review in the United Kingdom courts, seeking an annulment of the MCA's decisions to authorise SangCya on the basis that they are in breach of Community law on one or more of the following three grounds. First, it argues that the MCA was not entitled under point 8(a)(iii) to have regard to data submitted in respect of Neoral prior to the 10th anniversary of Neoral's first authorisation within the EU (the cross-reference issue). Secondly, it argues that the MCA was precluded, as a matter of law, from finding that SangCya was essentially similar to Sandimmun, thereby excusing SangStat from the requirement to demonstrate that its product was safe notwithstanding its lack of bioequivalence with Sandimmun (the essential simi-

larity issue). Thirdly, it argues that, even if otherwise lawful, the contested decisions should be annulled because they infringe the general principle of non-discrimination, that similar situations (in this case, the assessment of Neoral and SangCya) should not be treated differently in terms of the data required for authorisation unless such differentiation is objectively justified (the non-discrimination issue).

31. At first instance, Novartis' application for judicial review was dismissed. On appeal, however, the Court of Appeal has decided to stay the national proceedings and refer a number of questions to the Court. The first two questions, which relate to the cross-reference issue, are as follows:

'1. In considering a marketing authorisation for a new product (C) under [point 8(a)(iii)], referencing a product (A) authorised more than 6/10 years ago, is a national competent authority ever entitled to cross-refer, without consent, to data submitted in support of a product (B) which was authorised within the last 6/10 years?

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

(a) product B was authorised under the [point 8(a)] hybrid abridged procedure, referencing product A; and

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

32. As regards the first of those two questions, the Court of Appeal notes in the order for reference that under Article 5 of the Directive, a competent authority, when deciding upon an application, must consider both whether the medicinal product is safe and efficacious, and whether the applicant has submitted all the particulars and documents required by Article 4 of the Directive. In the Court of Appeal's view, when considering the former issue, it should be open to the competent authority to consider all the data in its possession, regardless of their source. The Court of Appeal therefore requests that, if the Court of Justice concurs, the answer to the first question referred should indicate that any restriction on the data to which the authority may make reference relates only to the latter part of Article 5.

33. The third question relates to the proper interpretation of the proviso, and is as follows:

'3. (a) Does the final subparagraph of [point 8(a)] ("the proviso") apply only to applications made under [point 8(a)(iii)] or to applications made under point [8(a)(i)] also?

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

34. Questions 4 and 5 seek clarification of the meaning of essential similarity:

'4. Can products ever be essentially similar for the purposes of [points 8(a)(i) and (iii)] when they are not bioequivalent, and if so in what circumstances?

5. What is the meaning of the term pharmaceutical form, as used by the Court in its judgment in Case C-368/96 *Generics*? In particular, do two products have the same pharmaceutical form when they are administered to the patient in the form of a solution diluted to a macro-emulsion, micro-emulsion and nano-dispersion respectively?'

35. The sixth and final question relates to the non-discrimination issue, and asks whether it is consistent with the general principle of non-discrimination for a national competent authority, faced with hybrid applications for marketing authorisations under point 8(a) referencing product A for two other products, neither of which is bioequivalent to product A:

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

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

36. The Court has received written observations from Novartis, SangStat, the United Kingdom, French, Danish and Portuguese Governments and from the Commission. Novartis, SangStat, the United Kingdom, Danish and Netherlands Governments and the Commission made oral submissions at the hearing.

Assessment

Questions 1 and 2 — the cross-reference issue

37. The first two questions raise the issue of when, if at all, a competent authority, considering an application made under point 8(a) in respect of a new product (product C), referencing a product (product A) which has been licensed for at least the 6 or 10 year period specified in point 8(a)(iii), may have regard without consent to data provided in respect of another product (product B) which has been licensed for less than 6 or 10 years.

38. The parties agree that a competent authority may have regard to all data in its possession, regardless of their source, when assessing the safety and efficacy of a medicinal product. The various approaches suggested by the submissions are therefore all consistent with the Directive's overriding objective of promoting public health.

39. Where the parties differ is as to whether, as the Court of Appeal suggests in the order for reference, a competent authority must also assess whether the applicant has submitted sufficient evidence to demonstrate that the product is safe and efficacious having regard to the requirements of Article 4, and, if so, whether the competent authority may at that stage take account of data provided in respect of product B. Three approaches can be distinguished.

40. On the first approach, advanced by the United Kingdom Government, a competent authority need not consider the adequacy of the evidence submitted in support of an application when deciding whether to grant a marketing authorisation. That is because, the United Kingdom argues, the expert assessors employed by a competent authority cannot realistically be expected, having used all available data to verify that a product is safe and efficacious, then to put those data out of their minds in order to determine whether the applicant has itself sufficiently demonstrated safety and efficacy.

41. In the United Kingdom's view, a competent authority may therefore rely on data submitted in respect of product B in order to authorise product C, a conclusion which accords with the Directive's primary objective of safeguarding public health, as well as with the objective of minimising unnecessary testing on humans and animals. It thus proposes that the first and second questions should both receive affirmative answers.

42. According to the second approach, favoured by Novartis, the competent authority must verify the adequacy of the evidence submitted by the applicant, and in so doing, may not cross-refer to data submitted in respect of product B, or in the alternative may do so only where products A and B are essentially similar.

43. Novartis' primary submission is that such cross-reference is never permitted, on the basis that it would be contrary to the wording of point 8(a)(iii), under which only data relating to a reference product authorised for at least 6 or 10 years may be used, and also that it would be inconsistent with the balance of objectives underlying the Directive, and in particular, the aim of ensuring that innovative firms are not placed at a disadvantage. Novartis therefore submits that the first question should be answered in the negative, with the consequence that the second question does not arise.

44. As an alternative submission, Novartis suggests that cross-reference is permitted only where products A and B meet in full the requirements of essential similarity to one another. Novartis derives support for its alternative submission from paragraph 55 of the Court's judgment in *Generics*, in which the Court held that the authorisation of a generic product could extend to additions or changes to the authorisation of its reference product as regards dosage form, dose and dosage schedule granted within the 6 or 10 year period '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'.

45. Novartis' alternative submission would support an affirmative answer to the first question, but a negative response to the second, given that a difference of bioavailability between products A and B would, in the light of Novartis' proposed solution to question 4, necessarily result in a finding that those two products lacked essential similarity.

46. The third approach, like the second, attributes to the competent authority an obligation to assess the adequacy of the particulars and documents submitted in support of the application. In contrast with the second approach, however, it allows the competent authority, when performing the latter assessment, to take account of data relating to product B even where that

product does not meet in full the requirements of essential similarity in relation to product A, provided that any lack of similarity relates to pharmaceutical form, therapeutic indication or dose, in other words the types of difference permitted under the proviso where appropriate bridging data have been supplied. In such circumstances, it is argued, products A and B should still be regarded as essentially the same reference product for the purposes of an application under the abridged procedures.

47. The third approach is favoured by SangStat, the Danish, French, and Netherlands Governments and the Commission. However, those parties differ somewhat in how they formulate the approach.

48. The Danish Government suggests that the *Generics* judgment should extend not only to all additions or changes to therapeutic indications, dosage forms, doses and dosage schedules authorised in respect of an essentially similar version of product A, but also to such additions and changes to product A which result in a variant product B lacking essential similarity with the original product.

49. The French Government, SangStat and the Commission prefer instead a formulation whereby cross-reference is permitted if product B constitutes a 'line extension' of product A. They draw in that regard on the most recent version of the Notice to Applicants [13] (in Volume 2A, chapter 1, at paragraph 4.2.2), which states that 'the requirement for authorisation for at least 6/10 years in the Community does not apply to line extensions used as reference products beyond the 6/10 years data exclusivity period of the original medicinal product'.

50. A line extension is defined by the Notice to Applicants (in volume 2A, chapter 1, at paragraph 5.2) as any variation on an original product which would fall within the scope of Annex II of Regulations No 541/95 [14] and 542/95, [15] except insofar as the variation involves the introduction of a new active substance.

13 — At the time when the submissions were prepared, the most recent version was that of May 2001. A subsequent version has since been introduced in November 2002, but the text has not been amended in any respect material to the present proceedings.

14 — Cited in note 10.

15 — Commission Regulation of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council Regulation (EEC) No 2309/93, OJ 1995 L55, p. 15.

51. The difference between the two formulations of the third approach is more apparent than real. The types of variation which are listed in Annex II to Regulations 541/95 and 542/95, and which would not involve the insertion of a new active substance, are changes to the therapeutic indication, changes to dose, pharmaceutical form and route of administration. The 'line extension' formulation would therefore permit cross-reference in the same circumstances as those specified by the Danish Government.

52. Similarly, both formulations in my view necessitate an acceptance that products A and B need not be essentially similar for cross-reference to be made to product B's data. This is because, with the exception of changes relating to therapeutic indication, the types of change by which product B may be differentiated from product A without preventing cross-reference to product B's data will exceed the limits of essential similarity as defined in the *Generics* case, given that variations to dosage will result in changes to the quantitative composition of a drug, that alterations to the form of dosage may affect pharmaceutical form, and that both types of change may have implications for bioequivalence. The Danish Government acknowledged as much in its written observations, whilst the Commission and SangStat accepted the point in their oral submissions before the Court.

53. It appears to me that the third approach is the correct one.

54. In my view, the Court of Appeal and the parties to the present case are right to assert that a competent authority may have regard to all available data, irrespective of their source, when verifying that a product is safe and efficacious. A competent authority must clearly be permitted to decline an application on the strength of data showing a product to be unsafe or lacking in efficacy even if those data were submitted in respect of another product and continue to enjoy protection pursuant to point 8(a)(iii).

55. However, it is in my opinion untenable to assert, as the first approach does, that, as a consequence of the freedom to refer to all data in verifying safety and efficacy, a competent authority cannot also perform a separate and independent assessment of an application in order to verify the adequacy of the documents and particulars submitted in support of that application. Such an approach would remove any element of data protection from the authorisation procedure and is therefore contrary to point 8(a)(iii).

56. It is also incompatible with the wording of Article 5, which requires the compe-

tent authority to verify the adequacy of the particulars and documents submitted in support of the application in accordance with Article 4. There is in my opinion no practical reason why a competent authority should not be able to perform that task after having first satisfied itself as to the safety and efficacy of a product.

57. I find the second approach equally unconvincing. On its primary submission, Novartis would deny the possibility of cross-referring to data submitted in respect of product B even when products A and B are essentially similar to one another. That submission appears to me flatly inconsistent with the Court's conclusions in *Generics*, which were based on the notion that the essential similarity of the original reference product and its subsequent variants rendered them the same product for the purposes of point 8(a)(iii). Following *Generics*, therefore, cross-reference to product B's data would undoubtedly be possible where product B was essentially similar to product A. To exclude the application of the *Generics* decision whenever a subsequently authorised variant of a reference product had been given a new designation would elevate form over substance, and would create an easy route for applicants to gain additional data protection in circumvention of *Generics*.

58. Novartis' alternative submission, which would allow cross-reference to product B's data only if products A and B were essentially similar, is consistent with *Generics*, but none the less appears to me to be unsatisfactory for the following reasons.

59. First, whether a modification of a reference product resulted in a new variant which remained within the bounds of essential similarity would not appear to correlate with the cost or difficulty involved in developing the modification and testing the variant. To accord access to data only where the limits of essential similarity had not been surpassed would therefore introduce an arbitrary distinction into the marketing authorisation regime.

60. Moreover, to limit the application of the *Generics* decision to cases where essential similarity could be shown between the original and the variant product would in practice largely confine it to new therapeutic indications, given the impact of dosage change on quantitative composition, dosage form on pharmaceutical form, and both such changes on bioequivalence.

61. The third approach therefore seems to me the most compatible with the scheme of the Directive as interpreted in the *Generics* judgment. It best succeeds in balancing the conflicting objectives of data protection and the avoidance of unnecessary testing on humans and animals by reserving additional data protection for the most significant modifications to an original product, namely those which involve the introduction of a new active substance. That approach is also consistent with, and supportive of, my Opinion delivered today in *AstraZeneca.* [16]

Question 3

62. The third question referred consists of two parts. Question 3(a) asks whether the proviso applies only to applications made under point 8(a)(iii) or to applications under point 4.8(a)(i) also. Question 3(b) asks whether essential similarity is a prerequisite for the use of the proviso.

63. It is not clear whether question 3(a) raises an issue of any practical significance. An applicant who had consent to use data relating to an essentially similar product would be able to submit and to rely on the probative value of those data as part of a new application under the normal procedure even if there were no possibility of making a hybrid abridged application with consent under point 8(a)(i).

64. In any event, I agree with France, the United Kingdom, SangStat and Novartis that the proviso can be relied upon in combination with either point 4.8(a)(i) or (iii). First and foremost, it is separated by a paragraph break from the text of point 8(a)(iii). Nor, furthermore, has any policy argument been advanced as to why it should not apply in combination with both provisions.

65. As to question 3(b), the Commission, the Danish and the United Kingdom Governments, Novartis and SangStat (having modified its position in its oral submissions) submit that the requirement for essential similarity is relaxed in the case of the hybrid abridged procedure laid down in the proviso. Only the French Government clearly maintains that essential similarity is a requirement under the proviso.

16 — Case C-223/01: see in particular paragraph 66 of the Opinion.

66. In my view, essential similarity in all respects is not required in order for an application to proceed under the proviso.

67. The purpose of the proviso is to allow an applicant whose product is essentially similar to an existing product except insofar as it differs in one or more of the respects stipulated by the proviso to submit additional or bridging data only with regard to that difference. The relaxation of the criterion of essential similarity in respect of the differences specified in the proviso is possible precisely because the proviso then requires additional bridging data to be submitted, thereby assuring that the safety and efficacy of the new product can none the less be assessed.

68. The interpretation of the proviso which I propose here accords with that adopted by the 1993 version of the Notice to Applicants. [17] Whilst subsequent versions of the Notice to Applicants have not explicitly endorsed such an interpretation, nor would they appear to have said anything to contradict it.

69. Any other reading of the proviso would render largely inapplicable two of the three categories of difference which it identifies given the definition of essential similarity laid down by the Court in the *Generics* judgment. A change to the dose of a medicinal product will preclude essential similarity, given that it will constitute a change to the quantitative composition of the product. Similarly, an alteration to the route of administration will in many instances amount to a modification of pharmaceutical form.

Questions 4 and 5 — the essential similarity issue

70. The fourth and fifth questions concern the meaning of essential similarity in point 8. Question 4 asks whether bioequivalence is always required for a finding that two products are essentially similar. Question 5 asks what is meant by pharmaceutical form, and more particularly whether products have the same pharmaceutical form where they are administered to the patient in the form of a solution diluted to a macro-emulsion, micro-emulsion and nano-dispersion respectively.

71. The questions relating to the essential similarity issue remain relevant to the resolution of the present proceedings despite the proposed answers to questions

17 — See the passage reproduced at paragraph 13.

1 and 2, given that even assuming the possibility of cross-referring to the data submitted in respect of Neoral, the validity of SangCya's marketing authorisation would none the less depend on its being shown either that SangCya is essentially similar to Neoral or Sandimmun or that appropriate bridging data have been submitted in accordance with the proviso.

72. As is clear from the Court's previous case-law, the starting point when interpreting the meaning of essential similarity, as with the other requirements laid down by point 8(a), must be to ensure that the requirements of safety and efficacy are at all times maintained in respect of applications pursuant to point 8(a)(i) and (iii) [18] through the specification of standards which are sufficiently precise and detailed to ensure a harmonised level of protection.

73. To that end, the Court in *Generics* adopted a definition of essential similarity drawn from the minutes of the meeting of the Council in December 1986 at which Directive 87/21 was adopted. As set out in the operative part of the judgment, its definition specifies bioequivalence together with pharmaceutical form and qualitative and quantitative composition as criteria which the competent authority of a Member State may not disregard when determining whether two products are essentially similar. Novartis, the Danish and Portuguese Governments, and the Commission accordingly submit that bioequivalence is a necessary requirement for essential similarity.

74. It is true, as the United Kingdom and SangStat point out, that the formulation contained in the Council's minutes and reproduced at paragraph 25 of the *Generics* judgment states that '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*'. [19] In reliance on the italicised passage, the United Kingdom and SangStat assert that bioequivalence is not an invariable requirement for a finding of essential similarity. I do not accept their interpretation of that passage. In my view, it is intended only to indicate that bioavailability studies will not always be required in order to demonstrate bioequivalence in cases where bioequivalence is in any event clear.

18 — See *Generics*, cited in note 4, at paragraph 22 of the judgment. See also Case C-440/93 *Scotia Pharmaceuticals* [1995] ECR I-2851, at paragraph 17.

19 — Emphasis added.

75. The United Kingdom Government and SangStat submit also that bioequivalence will not always be a relevant criterion in order to determine whether two products are equally safe and efficacious, and that therefore it should not constitute an inflexible requirement of essential similarity. Such is the case, they suggest, with cyclosporin products, given that doctors must regularly measure the levels of cyclosporin in a patient's blood and adjust doses accordingly. I am unconvinced, however, that it would not be necessary, at least when fixing for a patient the initial dosage of a new product claiming essential similarity to an existing product, to be confident of the two products' bioequivalence.

76. The United Kingdom further submits that in respect of certain types of product, the criterion of bioequivalence is inapplicable because they owe their therapeutic effect to topical application rather than transmission via systemic circulation. I find that submission equally unconvincing. It appears from the Community Guidelines relating to the investigation of bioavailability and bioequivalence that whilst the approach commonly used to determine systemic bioavailability cannot be employed in such cases, local availability may still be assessed using measurements quantitatively reflecting the presence of the active substance at the site of action, arrived at by methods specially chosen for the particular combination of active substance and localisation in question. [20]

77. It is therefore my opinion that bioequivalence is a necessary requirement of essential similarity.

78. As regards the proper meaning of pharmaceutical form, Advocate General Ruiz-Jarabo Colomer in the *Generics* case defined it, in my view correctly, as the combination of the form in which a pharmaceutical product is presented by a manufacturer (the form of presentation) and the form in which it is administered (the form of administration). [21] He drew the definition from the European Pharmacopoeia, inaugurated by the Council of Europe in 1964 for the purposes of laying down common standards for the composition and preparation of substances used in the manufacture of medicines. Applicants are required in a number of respects by the Annex to Directive 75/318/EEC to prepare the particulars and documents for submission pursuant to Article 4 of the Directive in accordance with the standards laid down by the European Pharmacopoeia.

79. The definition supplied by the European Pharmacopoeia does not, however, indicate with what degree of specificity the form of presentation and the form of administration must be described. It therefore does not in itself resolve the disagreement between the parties to the present proceedings as to whether the products in question may all be given the label of oral solution or whether it is instead necessary

20 — See the Guideline on Investigation of Bioavailability and Bioequivalence at paragraph 1, in volume 3C of the Community Guidelines.

21 — At point 37 of the Opinion.

to qualify them as solutions diluted for oral administration to a macro-emulsion, a micro-emulsion and nano-dispersion respectively.

80. As the Notice to Applicants indicates, further guidance may be obtained regarding the appropriate level of detail required by Community law from the European Pharmacopoeia list of standard terms. [22] It would appear from the file that the list does not distinguish between oral liquids depending upon whether on dilution they undergo a macro-emulsion, micro-emulsion or nano-dispersion process. On that basis, to insist upon such a level of detail would appear to exceed the requirements of Community law. Of the parties who address the issue, only Novartis asserts otherwise.

81. Such a conclusion appears consistent with the purpose of ensuring safety and efficacy which underlies the notion of essential similarity. Thus, the Commission submits that the pharmacokinetics (the time course of the absorption, distribution and excretion of the medicinal product) of oral liquid pharmaceutical forms is generally so similar that they deserve to be regarded as a single pharmaceutical form.

82. Novartis disagrees with the Commission, pointing out that differences between products resulting from their respective processes of dispersion or emulsion may affect their comparative bioavailability and may therefore impact upon their safety and efficacy. I am not, however, convinced of the relevance of Novartis' argument. Given that bioequivalence is in any event an independent requirement of essential similarity, it seems to me that the interpretation of pharmaceutical form need not be influenced by a concern to ensure bioequivalence.

83. In my opinion, therefore, the pharmaceutical form of a given product is the combination of the form of presentation and the form of administration of that product. Products administered orally in the form of a solution are to be regarded as having the same pharmaceutical form irrespective of whether they are diluted to a macro-emulsion, micro-emulsion or nano-dispersion.

Question 6 — the non-discrimination issue

84. By its sixth question, the Court of Appeal seeks to ascertain whether there is any breach of the general principle of non-discrimination for a competent authority, considering two hybrid applications referencing product A for two products, B and C, neither of which is bioequivalent to product A, to require full clinical data

22 — In volume 2A, chapter 1, paragraph 4.2.

relating to bioavailability in respect of product B as a condition of authorisation, but, having considered the data filed in support of product B, not to require the same data in respect of product C.

85. In my view, the sixth question does not raise any issue independent of those already discussed in relation to the preceding five questions. If the competent authority were otherwise entitled as a matter of Community law to rely on the data submitted in support of product B when considering the application in respect of product C, the applicant seeking authorisation of product C would not be similarly situated to the applicant seeking authorisation of product B, and the general principle of non-discrimination would be of no application. If, however, the competent authority were not otherwise entitled as a matter of Community law to rely on the data submitted in support of product B, the holder of the authorisation for product B could challenge any authorisation of product C on that basis, without resort to the principle of non-discrimination. Accordingly, in my opinion, an answer to the sixth question is not required in order to enable the referring court to proceed to a determination of the case.

Conclusion

86. I am therefore of the opinion that the questions referred for a preliminary ruling by the Court of Appeal of England and Wales (Civil Division) should be answered as follows:

(1) In considering whether to grant a marketing authorisation in respect of a new product under Article 4 of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions relating to medicinal products, a

competent authority may refer to all available data when assessing the safety and efficacy of that product.

If the application pertains to a new product C and is made under point 8(a)(iii) of the third paragraph of Article 4, making reference to a product A which was authorised more than 6/10 years previously, a competent authority is entitled, when verifying that the documents and particulars submitted in support of the application comply with Article 4, to cross-refer to data submitted in support of product B which was authorised within the previous 6/10 years, without consent of the person responsible for the marketing of product B, provided that products A and B are essentially similar or differ only in respect of their pharmaceutical form, dose, or therapeutic use.

(2) The proviso in the final subparagraph of point 8(a) of the third paragraph of Article 4 of Directive 65/65 applies to applications made under point 8(a)(i) and (iii) of that paragraph. In order for an application to be made under the proviso in respect of a new product C making reference to a product A, product C must be essentially similar to product A except insofar as it differs in one or more of the respects specified by the proviso.

(3) For two products to be essentially similar within the meaning of point 8(a) of the third paragraph of Article 4 of Directive 65/65, they must be bioequivalent.

(4) Pharmaceutical form is the combination of the form in which a pharmaceutical product is presented by the manufacturer and the form in which it is administered, including the physical form. Products administered orally to the patient in the form of a solution diluted to a macro-emulsion, micro-emulsion or nano-dispersion are all to be regarded as having the same pharmaceutical form.