JUDGMENT OF THE COURT OF FIRST INSTANCE (Fifth Chamber)
18 December 2003 *

In Case T-326/99,

Nancy Fern Olivieri, resident in Toronto (Canada), represented by N. Green QC and J. Marks, barrister, and R. Stein, solicitor, with an address for service in Luxembourg,

applicant,

v

Commission of the European Communities,

and

European Agency for the Evaluation of Medicinal Products,

* Language of the case: English.

represented by R. Wainwright and H. Støvlbæk, acting as Agents, with an address for service in Luxembourg,

defendants,

supported by

Apotex Europe Ltd, established in Leeds (United Kingdom), represented by P. Bogaert and G. Berrisch, lawyers, and G. Castle, solicitor, with an address for service in Luxembourg,

intervener,

APPLICATION for annulment of the Commission Decision of 25 August 1999 granting marketing authorisation for the medicinal product for human use known as Ferriprox-Deferiprone [C(1999) 2820] and of the revised Opinion of the European Agency for the Evaluation of Medicinal Products of 23 June 1999,

THE COURT OF FIRST INSTANCE
OF THE EUROPEAN COMMUNITIES (Fifth Chamber),

composed of: R. García-Valdecasas, President, P. Lindh and J.D. Cooke, Judges,

Registrar: J. Plingers, Administrator,

having regard to the written procedure and further to the hearing on 10 April 2003,

gives the following

Judgment

Legal context

A — *Relevant provisions of Regulation No 2309/93*

1 Article 11 of 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) provides:

'Without prejudice to other provisions of Community law, the authorisation provided for in Article 3 shall be refused if, after verification of the information and particulars submitted in accordance with Article 6, it appears that the quality, the safety or the efficacy of the medicinal product have not been adequately or sufficiently demonstrated by the applicant.

Authorisation shall likewise be refused if the particulars and documents provided by the applicant in accordance with Article 6 are incorrect...'

2 According to Article 6(1) of that Regulation:

'An application for authorisation for a medicinal product for human use must be accompanied by the particulars and documents referred to in Articles 4 and 4a of Directive 65/65/EEC, in the Annex to Directive 75/318/EEC and in Article 2 of Directive 75/319/EEC.'

3 According to Article 7(a) of Regulation No 2309/93 the Committee for Proprietary Medicinal Products, which is responsible — pursuant to Article 5 of that regulation — for formulating the opinion of the European Agency for the Evaluation of Medicinal Products on any questions concerning the marketing authorisation of a medicinal product for human use covered by that regulation, must, in order to prepare its opinion, verify 'that the particulars and documents submitted in accordance with Article 6 comply with the requirements of Directives 65/65/EEC, 75/318/EEC and 75/319/EEC' and also examine 'whether the conditions specified in [the] regulation for issuing a marketing authorisation for the medicinal product are satisfied'.

4 Article 13(2) of Regulation No 2309/93 provides:

'In exceptional circumstances and following consultation with the applicant, an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the Agency.

Such exceptional decisions may be adopted only for objective and verifiable reasons and must be based on one of the causes mentioned in Part 4 G of the Annex to Directive 75/318/EEC.'

B — *Relevant provisions of the Annex to Directive 75/318/EEC*

5 The text of the Annex to 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), to which various provisions of Regulation No 2309/93 refer, has been replaced by the Annex to Commission Directive 91/507/EEC of 19 July 1991 (OJ 1991 L 270, p. 32, hereinafter 'the Annex to the Directive').

6 According to the third paragraph of the introduction to the Annex to the Directive:

'All information which is relevant to the evaluation of the medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmacotoxicological or clinical test or trial relating to the medicinal product ...'.

7 Part 4 of that Annex lays down the requirements to be complied with by the particulars and documents accompanying applications for authorisation to market a medicinal product.

8 The third paragraph of Part 4 of the Annex to the Directive, relating to clinical documentation, provides:

'Evaluation of the application for a marketing authorisation shall be based on clinical trials including clinical pharmacological trials designed to determine the efficacy and safety of the product under normal conditions of use, having regard

to the therapeutic indications for use in human beings. Therapeutic advantages must outweigh potential risks.'

9 Part 4 A of that Annex provides:

'The clinical particulars to be provided pursuant to point 8 of Article 4(2) of Directives 65/65/EEC [or of Article 6(1) of Regulation No 2309/93, which refers to Article 4 of Directive 65/65] must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.'

10 Part 4 C of the Annex to the Directive sets out the information and documents relating to the presentation of the results of clinical trials and the requirements relating to them. Paragraph 1 of Part 4 C states as follows:

'The particulars of each clinical trial must contain sufficient detail to allow an objective judgment to be made:

...

— final report signed by the investigator and for multicentre trials, by all the investigators or the coordinating (principal) investigator.'

11 Part 4 G of that Annex deals with the documentation to be produced for applications for authorisation made in exceptional circumstances. It is worded as follows:

'When, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on the quality, efficacy and safety under normal conditions of use, because:

— the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence,

or

— in the present state of scientific knowledge comprehensive information cannot be provided,

or

— it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorisation may be granted on the following conditions:

(a) the applicant completed an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile;

(b) the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital ...;

(c) the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.'

Facts

A — *Thalassemia major and its treatment by deferoxamine or deferiprone*

12 Thalassemia major (also known as Cooley's syndrome) is an inherited disease characterised by severe anaemia, which affects an estimated 10 000 to 20 000 people in the European Union. Its treatment necessitates frequent blood transfusions. Such transfusions, however, result in an accumulation of iron in a patient's organs. Since the body has no natural means of eliminating excess iron, this gradual accumulation of iron in the organism causes damage, in particular to the heart and liver, which reduces the patient's life expectancy.

13 The principal pharmacological therapy available to counter iron overload is deferoxamine, which has existed for over 30 years. That treatment is uncomfortable, since it is administered by subcutaneous infusion, which must be carried out several times a week and may last up to 12 hours per day. It may also cause hypersensitivity to the substance.

14 Subsequently, another pharmacological treatment was developed to counter iron overload, namely, deferiprone, a product which has the advantage of being administered orally.

B — *Dr Olivieri's work on deferiprone*

15 The applicant, Dr Nancy Fern Olivieri, is an internationally recognised specialist in thalassemia major and is an established specialist in the area of treatment of that disease by deferiprone.

16 In 1989, in order to investigate the efficacy and safety of deferiprone, the applicant undertook a pilot study of 27 patients unwilling or unable to take standard therapy with deferoxamine. On the basis of the results of that trial, the applicant contemplated obtaining approval of that product in the United States and contacted the Food and Drug Administration (hereinafter 'the FDA') to ascertain what was necessary for that purpose. The FDA indicated that it would be necessary to carry out three clinical trials in order to evaluate the various aspects of deferiprone and that a private sponsor would have to be obtained to finance the research.

17 On the basis of those instructions, the applicant took part in the drawing up of protocols for each of the three trials required by the FDA, namely a trial to compare the efficacy and safety of deferiprone with deferoxamine (trial LA-01), a short-term trial to evaluate the adverse effects of deferiprone as understood at that time, namely bone marrow function and joint disease (trial LA-02), and a trial on the long-term efficacy and safety of deferiprone, which was the continuation of the pilot study (trial LA-03). Dr Olivieri was the principal investigator for trials LA-01 and LA-03 and was co-chairman of the steering committee for trial LA-02.

18 Each of the three clinical trials was financed by Apotex Research Inc., established in Weston (Canada), which had decided to participate in the financing of the work carried out by Dr Olivieri on deferiprone with effect from April 1993.

19 During the trials the applicant reached the preliminary conclusion that deferiprone was ineffective in almost half of the patients treated. She reported her concerns to the Review Ethics Board of the Toronto Hospital for Sick Children where she works, which advised her to report her concerns to the relevant authorities. The Board also concluded that a new clinical protocol to evaluate the continued efficacy of deferiprone was necessary and recommended in particular that she amend the information forms provided to patients in the trials to reflect concerns regarding the long-term effectiveness of deferiprone.

20 On 24 May 1996 Apotex decided to terminate the applicant's involvement in trials LA-01, LA-02 and LA-03 and to terminate prematurely trials LA-01 and LA-03, as it was entitled to do under the protocols to those trials. According to the report prepared by the independent commission of inquiry set up by the Canadian Association of University Teachers (J. Thompson, P. Baird and J. Downey, *The Olivieri Report*, James Lorimer & Co Ltd, Toronto, 2001) Apotex Research took that decision because Dr Olivieri was going to reveal to her

patients — in accordance with her ethical obligations — the risk linked to the low efficacy of deferiprone which she had discovered in the course of trial LA-01. It is also apparent from the inquiry carried out by the complaints committee of the Ontario College of Physicians and Surgeons and by the Dean of the Faculty of Medicine of the University of Toronto that, in so informing her patients, Dr Olivieri was not in breach of her ethical obligations.

21 In a subsequent study made without the financial support of Apotex Research, the applicant concluded that in addition to the doubts resulting from trials LA-01 and LA-03 as to the efficacy of deferiprone, there was additional evidence that the product was toxic to the heart and liver and that its use carried considerable risks of the development of cardiac disease and hepatic fibrosis, which exposed patients to an increased risk of premature death. As a result, the applicant discontinued trials of the product on humans. Those findings were presented in an article published on 13 August 1998 in the *New England Journal of Medicine* (Olivieri and others, 'Long-Term Safety and Effectiveness of Iron-Chelation Therapy with Deferiprone for Thalassemia Major', *New England Journal of Medicine*, vol. 339, No 7, pp. 417-423).

C — *The Community procedure for the grant of marketing authorisation for deferiprone*

22 On 6 February 1998 Apotex Europe Ltd ('Apotex') submitted an application to the European Agency for the Evaluation of Medicinal Products ('EMEA') under Article 4(1) of Regulation No 2309/93 for the granting of a marketing authorisation for the medicinal product subsequently called 'Ferriprox', the active ingredient of which is deferiprone. That medicinal product was the subject of the centralised authorisation procedure provided for in Regulation No 2309/93.

23 The three reports relating to trials LA-01, LA-02 and LA-03 were sent by Apotex with the application for marketing authorisation, but did not bear the applicant's signature.

24 In the course of the evaluation procedure, Apotex provided written and oral explanations. The Committee for Proprietary Medicinal Products ('CPMP'), which is required, pursuant to Article 5 of Regulation No 2309/93, to formulate the opinion of the EMEA, delivered an opinion on 27 January 1999 in favour of granting marketing authorisation for the medicinal product, having regard to exceptional circumstances referred to in Article 13(2) of Regulation No 2309/93 and Part 4 G of the Annex to the Directive ('the initial opinion').

25 That opinion was issued with an assessment report dated 27 January 1999 ('the first assessment report'), which was prepared by the CPMP to explain the different data taken into account in the evaluation procedure.

26 In the absence of any challenge by Apotex, the initial opinion was considered final and was transmitted by the EMEA to the Commission on 4 March 1999 in accordance with Article 9(2) of Regulation No 2309/93. That information was made public in April 1999. The Commission initiated the procedure provided for in Articles 10 and 73 of Regulation No 2309/93 and on 9 May 1999 the Standing Committee on Medicinal Products for Human Use delivered a unanimous favourable opinion on the Commission's draft decision.

27 Having become aware of the fact that the CPMP had issued a favourable opinion on 27 January 1999 regarding the application for marketing authorisation for deferiprone, the applicant, assisted by her legal advisers, sent a number of letters to the EMEA and to the members of the CPMP giving them her observations on the low efficacy and the cardiac and hepatic risks linked with that product. In particular, the applicant's letter of 28 April 1999 to the EMEA and to the

members of the CPMP set out the scientific grounds on which she based her opinion that the authorisation for deferiprone would lead to an increase in the risk of premature death for persons treated with it owing, in particular, to the progression of hepatic fibrosis and the development and progression of cardiac disease. Similarly, the letter from the applicant's legal adviser of 16 May 1999 to Professor Garattini, a member of the CPMP, sent supplementary information relating to the cardiac and hepatic toxicity of deferiprone. In the course of that correspondence, which was accompanied by several documents relating to the scientific evaluation of deferiprone which had not been sent by Apotex in the context of the initial evaluation procedure, the applicant also had the occasion to set out her version of the facts concerning the dispute between her and Apotex regarding, in particular, the conduct and the premature end of trial LA-01, for which she had been the principal investigator.

28 Following her intervention, the Chairman of the CPMP indicated to the Commission, in a letter of 28 May 1999, that he had received potentially important new information regarding the safety of deferiprone, primarily relating to the 'risk of progression of hepatic fibrosis even over a short period of time'. The letter also stated that that information would be rapidly reviewed in the light of the data previously submitted in order to determine whether the benefit-risk ratio was altered, and asked the Commission to explain the procedure by which any results of that analysis could be taken into consideration. Moreover, by letter of the same day, the CPMP requested Apotex to supplement its application for marketing authorisation with any additional available information or to confirm that all currently available information relevant to the risk of hepatic fibrosis had been submitted to the EMEA.

29 By letters of 26 May and 1 June 1999 Apotex submitted its observations on the documents submitted to the CPMP by the applicant, sent three papers presented at the Ninth International Conference on Oral Chelation which was held in Hamburg from 25 to 28 March 1999 (namely 'Sequential liver fibrosis grading during deferiprone treatment in patients with thalassemia major' by Galanello and Others; 'The assessment of liver fibrosis in thalassemia major during chelation therapy' by Piga and Others; and 'Liver iron overload in adult

thalassemia major patients under regular chelation therapy with desferrioxamine' by Cappellini and Others) and other supplementary documents and stated that it had sent all the relevant information to the CPMP.

30 By letter of 15 June 1999 the Commission informed the CPMP that the marketing authorisation procedure had been suspended pending additional scientific clarification of the information submitted by the applicant to the CPMP, which appeared to be such as to call in question the safety of the medicinal product and required further examination. That letter also stated that 'it would be unreasonable and against the aims and purposes of Regulation (EEC) No 2309/93 to grant a marketing authorisation under such circumstances without further scientific clarifications'.

31 On 21 June 1999 an Ad-Hoc Expert Working Group ('the Expert Group'), convened at the request of the CPMP, met to discuss the new information concerning the safety of the product sent by Dr Olivieri and Apotex.

32 In the minutes of that meeting drawn up on 23 June 1999 ('the conclusions of the Expert Group'), the Expert Group stated that the new data was inconclusive as to the relationship between deferiprone and hepatic fibrosis. On that basis, the Expert Group considered that there was no need to reconsider the favourable opinion recommending the grant of a marketing authorisation in exceptional circumstances. It therefore proposed to retain the restricted indication; to inform the physician about the inconclusive nature of the relationship between hepatic fibrosis and deferiprone and to recommend monitoring in a specific subpopulation with hepatitis C; to request Apotex to confirm in writing that it would provide the sales figures in each Member State to ensure that deferiprone is not prescribed other than for the approved indication; and to obtain more information from Apotex and other sources as soon as that information became available.

33 By letter of 23 June 1999 Apotex agreed to give the additional undertakings, in particular with regard to the supply of sales figures of Ferriprox in each Member State.

34 In view of the recommendations of the Expert Group, the CPMP decided to retain the initial opinion in favour of granting marketing authorisation for Ferriprox in exceptional circumstances. However, it recommended a revision of the draft summary of the technical characteristics of the product and of the package leaflet in order to extend the information with regard to the risk of hepatic fibrosis. The CPMP adopted a revised opinion on 23 June 1999 ('the revised opinion'), of which the EMEA informed the Commission on 7 July 1999.

35 That opinion was accompanied by an assessment report dated 23 June 1999 ('the supplementary assessment report'), which was prepared by the CPMP to explain the different data taken into account by the CPMP in the evaluation procedure.

36 The revised opinion was incorporated by the Commission into a new draft decision and after the Standing Committee on Medicinal Products for Human Use, referred to in Article 73 of Regulation No 2309/93, had delivered a favourable opinion on that draft on 13 August 1999, the Commission adopted, on 25 August 1999, the decision granting marketing authorisation for the medicinal product for human use, Ferriprox ('the contested decision'), which was notified to Apotex on 2 September 1999. In accordance with Article 12(3) of Regulation No 2309/93, notification of the marketing authorisation was published in the *Official Journal of the European Communities* on 24 September 1999 (OJ 1999 C 270, p. 2).

37 On 25 August 1999, pursuant to Article 12(4) of Regulation No 2309/93, the EMEA also made available the European Public Assessment Report (EPAR) ('the public assessment report') in order to explain the grounds for its favourable opinion regarding the issue of the marketing authorisation. That report is the public version of the reports previously drawn up by the CPMP in the context of

the scientific evaluation of the request for marketing authorisation, namely the first assessment report and the supplementary assessment report.

Procedure and forms of order sought

38 By application lodged at the Registry of the Court of First Instance on 19 November 1999, the applicant brought the present action for annulment of the revised opinion and of the contested decision.

39 By separate document lodged the same day, the applicant lodged an application for the suspension of the contested decision.

40 By order of 7 April 2000 in Case T-326/99 R *Fern Olivieri* v *Commission* [2000] ECR II-1985, the President of the Court of First Instance rejected the application for the suspension of the contested decision ('the interim order').

41 On 8 February 2000 Apotex sought leave to intervene in the main proceedings in support of the Commission and of the EMEA. That application was notified to the parties, who submitted their observations within the prescribed period. By order of 14 March 2000, the Court (Fifth Chamber) granted Apotex leave to intervene.

42 By document lodged on 22 March 2000, the Commission and the EMEA raised a plea of inadmissibility in accordance with Article 114(1) of the Rules of Procedure of the Court of First Instance. On 10 May 2000 the applicant and Apotex submitted their observations on that plea of inadmissibility. By order of

15 June 2000, the Court (Fifth Chamber) decided to join the plea of inadmissibility and its examination of the merits of the case.

43 Upon hearing the report of the Judge-Rapporteur, the Court decided to open the oral procedure and on 26 November 2002, by way of measures of organisation of the procedure, the parties were requested to submit several documents and to reply in writing to a number of questions.

44 The measures thus directed by the Court were complied with: by the applicant by letter of 3 February 2003; the Commission by letter of 31 January 2003; and Apotex by letter of 3 February 2003.

45 The parties presented oral argument and replied to the questions of the Court at the hearing on 10 April 2003.

46 The applicant claims that the Court should:

— annul the Commission Decision of 25 August 1999 [C (1999) 2820];

— annul the CPMP's revised opinion of 23 June 1999;

— order the Commission to pay the costs.

47 The Commission and the EMEA contend that the Court should:

— reject the application as inadmissible or, failing that, as unfounded;

— order the applicant to pay the costs.

48 Apotex contends that the Court should:

— reject the application as inadmissible or, failing that, as unfounded;

— order the applicant to pay the costs.

Law

A — *Admissibility of the application for annulment of the revised opinion*

Arguments of the parties

49 The applicant submits that Article 230 EC does not contain an exhaustive list of the institutions whose acts are amenable to review (Case 294/83 *Les Verts* v *Parliament* [1986] ECR 1339, paragraphs 21 and 23) and that the EMEA is an

'auxiliary body vested with specific powers of an administrative nature' whose acts must be capable of being the subject of an action for annulment (Joined Cases 193/87 and 194/87 *Maurissen and European Public Service Union* v *Court of Auditors* [1989] ECR 1045, and the Opinion of Advocate General Darmon in that case, at point 54). She also submits that it is necessary to examine the effects of the CPMP's opinion in order to find out whether or not it is amenable to review (Case 22/70 *Commission* v *Council* [1971] ECR 263). She submits that the CPMP's opinion is the culmination of a special procedure (Joined Cases 8/66 to 11/66 *Cimenteries and Others* v *Commission* [1967] ECR 75) and observes that while Article 10(1) of Regulation No 2309/93 states that the Commission is not bound by that opinion, it is rarely in a position to contradict the CPMP and it most often decides to follow it.

50 The Commission and the EMEA, supported by Apotex, submit that the revised opinion is not an act which may be challenged under Article 230 EC. That article states that opinions cannot be challenged in proceedings for annulment and does not include the EMEA in the list of bodies whose acts are subject to review. They also submit that the revised opinion was merely a preparatory measure for the Commission's decision regarding the request for marketing authorisation. It corresponds to a stage in the decision-making process which is not binding on the Commission and neither creates rights nor imposes obligations on the applicant, to whom it is not of direct and individual concern.

Findings of the Court

51 In order to assess whether the applicant's application for annulment of the revised opinion is admissible it is necessary to decide whether that opinion is a preparatory act, that is to say, an 'intermediate measure whose purpose is to

prepare for the final decision'. Such an act may not be challenged under Article 230 EC (Case 60/81 *IBM* v *Commission* [1981] ECR 2639, paragraph 10).

52 The first subparagraph of Article 10(1) of Regulation No 2309/93 provides that 'within 30 days of receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking account of Community law'. The third subparagraph of Article 10(1) states that the draft decision may depart from the terms of the opinion, provided that the Commission gives a detailed explanation of the reasons for the differences.

53 The revised opinion is therefore an intermediate measure whose purpose is to prepare for the marketing authorisation decision. It is a preparatory measure which does not definitively lay down the Commission's position and is therefore not a challengeable act within the meaning of the case-law cited above.

54 As a result, the application for annulment of the revised opinion must be declared inadmissible.

55 However, in the present case the contested decision purely and simply confirms the revised opinion, to which it refers in its fourth recital. The content of that opinion, and also that of the assessment reports upon which it is based, are therefore an integral part of the statement of reasons for the contested decision, with regard in particular to the scientific assessment of deferiprone carried out by the CPMP and its rapporteurs. The content of the revised opinion must therefore be examined in the context of the application for annulment of the contested decision.

B — *The admissibility of the application for annulment of the contested decision*

Arguments of the parties

56 The applicant submits that the contested decision is of direct and individual concern to her for the purposes of the fourth paragraph of Article 230 EC. In substance, she submits that she was legitimately involved in the administrative procedure, as she drew the attention of the EMEA to the presence of a serious doubt regarding the scientific assessment of deferiprone and as she is the only person in a position to guarantee the authenticity of certain clinical trial reports on which the contested decision is based. Moreover, those reports were presented in an incorrect manner by the applicant for the marketing authorisation.

57 Furthermore, the applicant submits that she has an interest in bringing the present case because she is seeking to protect public health and the health of patients suffering from thalassemia; in view of her participation in trials LA-01 and LA-03, she is the only person in a position to protect that interest. She submits that none of the three reports relating to those trials submitted by Apotex with the application for marketing authorisation bear her signature, even though that is an essential safeguard for public health (see the interim order, paragraphs 65 and 66). Moreover, the applicant submits that, unlike the applicants in Case T-183/97 *Micheli and Others* v *Commission* [2000] ECR II-287, her clinical abilities were indeed taken into account and her interpretation of the results of trials LA-01 and LA-03 was criticised in the contested decision through the reference in it to alleged protocol violations. That also establishes her interest in bringing proceedings in order to safeguard her professional reputation.

58 The Commission and the EMEA, supported by Apotex, submit that the application is inadmissible for want of an interest in bringing proceedings. The applicant's professional reputation cannot constitute a genuine legal interest for the purposes of this case (*Micheli and Others* v *Commission*, paragraph 40).

59 As regards the question whether the decision is of individual concern to the applicant, the Commission and the EMEA, supported by Apotex, point out that where the applicant, as in this case, is not the addressee of the decision, she may claim that it is of individual concern to her only if she has a right to participate in the procedure for adopting the decision, in order to have her own interest taken into account by the Commission (see, in particular, Case 169/84 *Cofaz and Others* v *Commission* [1986] ECR 391, paragraphs 23 to 25). In the absence of such a right, the Court will refuse to recognise that the applicant has *locus standi* (order of the Court of 9 August 1995 in Case T-585/93 *Greenpeace and Others* v *Commission* [1995] ECR II-2205).

60 In the present case, the Commission and the EMEA observe that Regulation No 2309/93 provides for the involvement of only the applicant for marketing authorisation, the EMEA, and its scientific body, the CPMP, together with the Commission and the Member States. It does not confer on other persons or entities a right to participate in the procedure. Consequently, the fact that the applicant took part as researcher in some of the clinical trials concerning deferiprone and the fact that on her own initiative she informed the CPMP of her views about the efficacy and safety of that product do not suffice to distinguish her individual interest, she having no personal right to be heard or to have her interest taken into account (order of the Court of 3 June 1997 in Case T-60/96 *Merck and Others* v *Commission* [1997] ECR II-849).

61 The Commission and the EMEA submit that the obligation imposed on the investigator to sign the report on the clinical trial carried out by him, in accordance with Part 4 C.1 of the Annex to the Directive, is not a 'procedural guarantee' which can distinguish Dr Olivieri individually within the meaning of the judgment in *Cofaz and Others* v *Commission*. The purpose of that signature is not to have the investigator's interest taken into account but simply to guarantee the authenticity of the report.

62 Similarly, although the Commission and the EMEA acknowledge that the CPMP did indeed take the view that the product safety information sent by the applicant was potentially important (in particular the information in the letter of the CPMP

to the Commission of 20 May 1999), which was the reason for convening the Expert Group, they nevertheless submit that the exchanges with Apotex following the communication of that information (in particular the CPMP's letter to Apotex dated 20 May 1999 and Apotex's replies dated 26 May and 1 June 1999) do not suggest that the applicant has any procedural guarantee under Regulation No 2309/93 so as to distinguish her individually in relation to the contested decision.

63 Furthermore, the Commission and the EMEA, supported by Apotex, submit in essence that, even if there were a risk to the applicant's reputation because of negative assessments of her work allegedly made in the context of the contested decision, that would not give her *locus standi* to challenge the contested decision, as Article 68 of Regulation No 2309/93 does not allow the Commission to take such matters into account when deciding on marketing authorisations (Case 301/82 *Clin-Midy and Others* [1984] ECR 251, paragraphs 10 and 11; Case C-83/92 *Pierrel and Others* [1993] ECR I-6419, paragraph 21, and Case C-127/95 *Norbrook Laboratories* [1998] ECR I-1531, paragraph 108). Any supposed risk to the applicant's reputation or professional standing cannot therefore render the application admissible (*Micheli and Others* v *Commission*).

64 With regard to the question whether the decision is of direct concern to the applicant, the Commission and the EMEA submit that it is clear from the case-law that a decision is of direct concern to an individual only where its application does not depend on the exercise of a discretionary power by a third party (Case 55/86 *Arposol* [1988] ECR 13, paragraph 13). In essence, there must be a direct link between the Community measure and the person who contests it. However, in the present case, no evidence has been adduced to show that Apotex's application was based on the applicant's research or to show that the contested decision had an immediate effect on the assessment of the quality of her work and, potentially, on her capacity to obtain funding for her research. In any event, even if such evidence were adduced, it would not show that the applicant was directly concerned. Any effect on her professional reputation could only be

the result of interpretation by other members of the scientific community, who would make a personal assessment of the facts and take into account a multitude of factors.

65 Apotex observes that the applicant cannot bring an action for annulment as a representative of the interests of patients suffering from thalassemia major, since she is not the representative of those patients or of a patient organisation but a doctor. She merely makes reference to her medical activities in Canada but does not indicate how the approval of Ferriprox in the Community can have any effect on her patients. Apotex also submits that the health interests of patients cannot be directly affected by a marketing authorisation, as Ferriprox is issued only on prescription. Thus, Apotex must first decide to market the product and each doctor would then have to prescribe it to his patient.

Findings of the Court

66 It is necessary first to examine whether the applicant has an interest in bringing an action, because, if she has no such interest, it will be unnecessary to examine whether the contested decision is of direct and individual concern to her within the meaning of the fourth paragraph of Article 230 EC (*Micheli* v *Commission*, paragraph 34).

67 The applicant asserts that she has two types of interest in bringing the present action: to protect public health and to defend her professional reputation.

1. The applicant's interest in bringing an action in order to protect public health

(a) General considerations

68 First of all, pursuant to Article 152 EC (formerly the first subparagraph of Article 129(1) of the EC Treaty), a high level of human health protection is to be ensured in the definition and implementation of all Community policies and activities. That provision implies that the Community institutions must ensure that their decisions are taken in the light of the best scientific information available and that they are based on the most recent results of international research (Case T-13/99 *Pfizer Animal Health* v *Council* [2002] ECR II-3305, paragraph 158, and Case T-70/99 *Alpharma* v *Council* [2002] ECR II-3495, paragraph 171).

69 The Court points out that pursuant to Article 11 of Regulation No 2309/93 the Commission, before authorising the placing of a medicinal product on the market, must verify that the particulars and documents provided by the applicant for authorisation are indeed correct and that they adequately demonstrate the quality, safety and efficacy of that product. According to the third recital to Regulation No 2309/93, the Commission's decision to grant a marketing authorisation must be taken in the interest of public health, based on the objective scientific criteria of the quality, the safety and the efficacy of the medicinal product concerned, to the exclusion of economic or other considerations.

70 To enable the Commission to comply with those obligations, Regulation No 2309/93 and the documents to which it refers lay down precise rules for the presentation of applications for marketing authorisation, their investigation and subsequent decisions. In particular, Article 6(1) of Regulation No 2309/93 provides that 'an application for authorisation for a medicinal product for human use must be accompanied by the particulars and documents referred to in

Articles 4 and 4a of Directive 65/65/EEC, in the Annex to Directive 75/318/EEC and in Article 2 of Directive 75/319/EEC'. Pursuant to that provision, an applicant for marketing authorisation must annex to his application all the information relating to the scientific evaluation of the medicinal product in question, and in particular information concerning the results of all the clinical trials, whether favourable or unfavourable to the product (see the third paragraph in the introduction and Part 4 A of the Annex to the Directive). Compliance with the requirements set out in Article 6(1) of that regulation is vital to ensure attainment of the essential objective of safeguarding public health (interim order, paragraph 66, see also, by analogy, *Norbrook Laboratories*, paragraphs 40 and 41).

71 With regard more particularly to the question of the signature of the clinical trial reports, the Court points out, as has the Commission, that the statement in Part 4 C.1 of the Annex to the Directive — namely that the final report of such a trial must be signed by the investigator and, for multicentre trials, by all the investigators, or failing that, by the principal investigator — makes it possible to ensure the authenticity of the report which the applicant for marketing authorisation is required to send to the Commission.

72 The application of those provisions must, in principle, enable the Commission to comply with its obligations under Article 11 of Regulation No 2309/93 without, as a rule, having to obtain or verify information relating to the scientific evaluation of the medicinal product in question from or by persons other than the applicant for marketing authorisation.

73 Nevertheless, the Court notes that none of the provisions of the applicable Community rules prohibits the Commission, prior to granting a marketing authorisation, from following a procedure during which persons other than the applicant for marketing authorisation are able to submit their observations so as to enable it to fulfil its duty to check, in the interest of public health, that all the information relating to the scientific evaluation of the product in question, whether it be favourable or unfavourable to the product, has indeed been made

available to it. The fact that those rules do not contain any provision to that effect cannot prevent the Commission from obtaining information from a third party where such a course of action is indispensable in order to safeguard public health.

(b) The examination of the information sent by the applicant to the CPMP and the Commission

74 It is first necessary to examine the role played by the applicant in the various stages of the procedure for the scientific assessment of deferiprone in order to determine whether she has any interest in bringing this case.

75 At the initial stage, that is to say, until the applicant's intervention in the scientific assessment procedure, Dr Olivieri's role is distinguished principally by the fact that her work on deferiprone forms an essential part of the information relating to the scientific assessment of that product (see paragraphs 15 to 21 above).

76 Following the application for marketing authorisation, the Commission considered authorising the marketing of deferiprone, having taken into consideration only the information provided by Apotex and examined by the CPMP in the course of the initial assessment procedure.

77 It was then that the applicant sent to the CPMP information which led to the reopening of the scientific assessment procedure (see paragraphs 27 to 30 above).

78 The Court points out that the Commission suspended the marketing authorisation procedure on its own initiative and requested the CPMP to obtain additional scientific clarification. Such a step is justified by the fundamental aim of safeguarding public health, which constitutes the framework for the Commission's work. As set out above, the Community rules require the Commission to confirm that the particulars and documents provided by the applicant for marketing authorisation are correct in order that it may assess the quality, safety and efficacy of that product and authorise its marketing.

79 At that stage of the assessment procedure, the applicant could thus rely on the interest of protecting public health when she communicated to the CPMP additional information which might call in question the initial scientific assessment, given that the information provided by Apotex with its application for marketing authorisation or during the assessment procedure had been incomplete. The applicant was also entitled to send her own analysis of the results of clinical trial LA-01, inasmuch as she took the view that the account prepared by Apotex without her agreement was incorrect.

80 Consequently, in a situation in which, as in this case, the information furnished by the applicant directly to the CPMP is of such a nature as to call into question the initial scientific assessment of the medicinal product in question, as the Commission expressly recognised in its letter of 15 June 1999, and in which the person responsible for the authenticity of the final reports relating to some of the clinical trials disputes the veracity of information sent without her agreement by the applicant for marketing authorisation, the Commission is required, in the interest of public health, to examine that information. If it does not do so, the Commission ceases to be in a position to fulfil its obligations under Regulation No 2309/93.

81 The Court finds that the applicant therefore played an essential role in the work towards the perfecting of deferiprone and that the information which she sent to the CPMP enabled the Commission to confirm, in the interest of public health,

that the particulars and documents on the basis of which the marketing authorisation was authorised were both complete and correct. In those specific circumstances, a Commission decision addressed to the applicant would have been of concern to her if it had refused to examine the information provided by her in the course of the procedure for the scientific assessment of deferiprone or there had been an implicit decision to reject that information, which would have been the case if the Commission had adopted the decision to grant marketing authorisation without having examined that information. She would have been entitled to contest the legality of either of those decisions before the Court of First Instance.

82 However, following Dr Olivieri's involvement, the suspension of the marketing authorisation procedure and the Commission's decision to request a further examination, the initial scientific assessment of deferiprone was amended and supplemented by the CPMP. In the light of the contested decision and the opinions and reports on which it is based, none of the arguments submitted by the applicant in the course of the present proceedings supports the claim that the Commission failed to take into account the information directly communicated by the applicant in the course of the assessment procedure.

83 At the end of the scientific assessment, the CPMP, followed on this point by the Commission, justifies the marketing authorisation for deferiprone on the following grounds:

— first, the indication of deferiprone is strictly limited to the treatment of iron overload in patients who present thalassemia major and for whom treatment by deferoxamine is counter-indicated or is accompanied by severe toxicity;

— second, deferiprone is relatively effective, in the sense that it promotes elimination of iron and may prevent its accumulation in certain patients treated with it, as is shown by the results obtained by reference to the concentration of serum ferritin in the course of trials LA-01, LA-02 and LA-03 in particular;

— third, despite the information indicating the lower efficacy of deferiprone compared with deferoxamine and the lack of information showing that a negative iron balance is achieved in the long-term, the marketing authorisation for deferiprone is explained by the absence of another therapeutic solution able to preserve the life of the patients concerned by the indication;

— fourth, in order to obtain the information deemed necessary to complete the scientific assessment of deferiprone, the marketing authorisation is subject to a number of specific obligations requiring Apotex to supply additional information.

84 As regards the effects of deferiprone on the heart, Dr Olivieri sent directly to the CPMP or to its members various information relating to that issue, and in particular the finding that in 32% of patients treated with deferiprone in the course of trial LA-01 the iron overload was new or became worse. It is apparent from the file that this information was taken into account during the scientific assessment of deferiprone. The summary of product characteristics, contained in Annex I to the contested decision, alerts the treating physician by indicating that the data available is limited as regards the effect of deferiprone on cardiac function. Similarly, in order to obtain such data, the contested decision requires Apotex to supply, as one of its specific obligations, additional comparative data on survival and cardiac insufficiency, as well as data relating to the MRI assessments obtained in the course of trial LA-01. The Court points out in that

regard that the obligation relating to the MRI data is intended to remedy the fact — as was acknowledged by Dr Olivieri at the hearing — that this data had not been sent to the CPMP by her, even though she was in possession of it, and had refused to send it to Apotex.

85 With respect to the effect of deferiprone on the liver, Dr Olivieri sent directly to the CPMP various information in that regard, in particular as regards the risk of premature death caused by the progression of hepatic fibrosis. It is apparent from the file that this information was considered by the CPMP and the Expert Group in the course of the additional assessment procedure. The summary of product characteristics, which is contained in Annex I to the contested decision, was altered, in comparison with the initial draft, in order to take better account of the effects of deferiprone on hepatic function and in particular to warn the treating physician that there is still doubt as to whether deferiprone may worsen hepatic fibrosis and that there is an association between hepatic fibrosis and hepatitis C in thalassemia patients. Furthermore, the contested decision requires Apotex to supply additional data on hepatic fibrosis in approximately 30 patients treated with deferiprone over a period of four years.

86 With regard to the concentration of iron in the liver, the applicant sent directly to the CPMP the relevant results obtained in the course of trial LA-01. It is apparent from the file that those results were assessed during the supplementary examination carried out by the Rapporteur and Co-rapporteur of the CPMP and confirmed by the Commission in the contested decision. Moreover, the contested decision requires Apotex to supply additional data on efficacy and safety after four years of treatment with deferiprone of approximately 100 patients suffering from thalassemia. In those circumstances, the existence of the protocol violations alleged by Apotex and the statement in the public assessment report — based on a finding made in the course of the initial assessment — that the protocol for trial LA-01 had not been followed satisfactorily can have no bearing on the scientific assessment of the CPMP, which in fact gave its opinion on the basis of the results supplied by Dr Olivieri.

87 Moreover, Dr Olivieri informed the CPMP directly of her doubts regarding the risk associated with the marketing of deferiprone, which might be prescribed outside its indications and thus threaten a patient's vital process. It is apparent from the file that this risk was taken into account in the course of the assessment procedure. The conclusions of the Expert Group and the supplementary assessment report show that the applicant's concerns relating to that risk, as set out in her letter of 28 April 1999, were examined in the course of the scientific assessment and that they led to the adoption of monitoring measures in order to meet that concern. Thus the CPMP asked Apotex to undertake to send the total sales figures for each Member State during the year following the decision granting marketing authorisation, which Apotex agreed to do in its letter of 23 June 1999. In that regard, the Court points out that in response to questions put in the course of measures of organisation of the procedure the Commission stated — and the applicant did not dispute — that the sales of Ferriprox by Apotex covered the needs of approximately 1 400 patients out of the 2 000 who, according to the Commission, are capable of being treated with deferiprone.

88 Consequently, it is clear from the above that the information sent by the applicant directly to the CPMP was in fact examined and taken into account during the additional assessment procedure: some of that information led to a change in that assessment, whereas other information had already been taken into account in order to restrict the therapeutic indications for deferiprone or to form the subject of specific obligations imposed upon Apotex in the contested decision.

89 With regard to the particulars supplied by Apotex in its application for marketing authorisation, the applicant has no grounds for claiming that the CPMP and the Commission did not check the correctness and completeness of those particulars. The applicant's claim has no factual basis, given that it was precisely following her intervention and the Commission's request to reopen the assessment procedure that the CPMP, by letter of 20 May 1999, queried the completeness of the scientific information accompanying the application for marketing authorisation and supplied during the initial assessment procedure, and that the CPMP and the Expert Group, after examining the information sent by Apotex — in reply to the CPMP's letter of 20 May 1999 — and by the applicant, concluded that it was not necessary to reconsider the initial opinion in

favour of issuing a marketing authorisation, other than in order to clarify the risk relating to hepatic fibrosis and to take into account the risk of prescribing deferiprone when not indicated.

90 Similarly, the applicant cannot claim that there is a formal defect solely because she did not sign the report of clinical trial LA-01 (or the report of clinical trial LA-03) sent with the application for marketing authorisation submitted by Apotex. Although the applicable rules provide that the final report of a clinical trial must be signed by the investigators or the principal investigator (see Part 4 C.1 of the Annex to the Directive), it is also apparent from those rules that in the event of an incomplete or interrupted trial all the relevant information relating to that trial must be supplied with the application for marketing authorisation (see the introduction to the Annex to the Directive). Having regard to the termination of trials LA-01 and LA-03, the applicant's signature on the reports of those trials — which were accompanied by explanations as to why Apotex had decided to terminate them — was not formally required by the relevant rules. Moreover, it is clear from the data in the present case that the applicant provided the CPMP with all the particulars necessary to guarantee the authenticity of the results obtained in the course of trial LA-01.

91 Therefore, the Court finds that, although the applicant was entitled to make sure that the CPMP and the Commission examined the information which she had sent directly to the CPMP in order to contribute to the scientific assessment of deferiprone and to ensure the authenticity of the results obtained in the course of trial LA-01, that right ended at the moment when that information was examined and taken into account in the course of that assessment procedure.

92 Consequently, the applicant no longer has an interest in bringing proceedings to contest the legality of the contested decision is so far as concerns the examination of the correctness and completeness of the scientific information relating to deferiprone.

(c) The scientific assessment by the CPMP which was confirmed by the Commission

93 Unlike Apotex, the applicant for marketing authorisation and, as such, addressee of the contested decision, Dr Olivieri cannot claim entitlement to challenge, in an action for annulment, the scientific evaluation made by the CPMP and confirmed by the Commission. Admittedly, Dr Olivieri was particularly well qualified to supply the CPMP with important and relevant information because of her status as an acknowledged specialist in thalassemia major and her significant contribution to the research on which Apotex's application was based. Moreover, the Commission was required, in the interest of public health, to take into consideration and carefully evaluate the scientific data and the opinions which she had sent to it. However, in the context of the rules applicable to marketing authorisations, her role cannot be treated as equivalent to that of an applicant for marketing authorisation, who participates in the administrative procedure by virtue of a right which those rules have conferred on it. Dr Olivieri's participation in the assessment procedure is therefore confined solely to the production of relevant information relating to deferiprone and does not extend to the scientific assessment of that data for the purpose of authorising the marketing of that product. That task falls exclusively to the Commission under the procedures established by Regulation No 2309/93.

94 Unlike other Community administrative procedures, in particular those in the area of the competition rules, during which third parties, that is to say parties interested in or potentially affected by any Commission decision, are entitled to be heard by the Commission before the decision is adopted, Regulation No 2309/93 establishes a purely bilateral procedure. It is a procedure between the applicant for marketing authorisation and the administration, during which the administration must take into account the applicant's interest in obtaining marketing authorisation and the public interest in the protection of human health. Dr Olivieri, in her capacity as third party, is not entitled to participate in that procedure or set herself up as interlocutor of the CPMP and of the Commission in regard to the assessment of the scientific data relating to the product in question.

95 As a result, the applicant has no interest in bringing proceedings to challenge the legality of the contested decision in order to protect public health in so far as concerns the scientific assessment of deferiprone.

2. The applicant's interest in bringing proceedings in order to defend her professional reputation

96 Dr Olivieri also submits that she has an interest in bringing proceedings in order to defend her professional reputation. She claims that it was called into question in the contested decision, which dismissed certain results obtained in the course of trial LA-01 on the ground that they had given rise to protocol violations.

97 However, it is apparent from the file that, contrary to what Dr Olivieri may believe, her professional reputation was an important factor in the scientific assessment procedure performed by the CPMP, as has been indicated above (see, in particular, paragraphs 78 to 81). Thus, it is because of the role she played in the work relating to the finalisation of the product and her professional reputation that the observations which she had sent directly to the CPMP resulted in the reopening of the assessment procedure, the convening of the Expert Group, and the amendment of the draft decision. The mere fact that, after the scientific assessment, marketing authorisation was granted to Apotex despite her critical observations, in no way implies a negative appraisal of her professional reputation or a rejection of her own scientific assessment. The Court points out in that regard that the decision which the Commission was called on to adopt did not require it to decide on whether or not the two contradictory propositions put forward by Apotex and Dr Olivieri were correct. The CPMP and the Commission had to carry out an examination in which they weighed up, on the one hand, the interest of Apotex in marketing the product and the benefits which it might confer on those suffering from thalassemia major and, on the other hand, the potential risks for human health identified by the scientific assessment during the

procedure. The fact that the CPMP and, subsequently, the Commission, pronounced in favour of Apotex and, in so doing, in favour of patients who might benefit from the medicinal product does not mean that they found that the risks identified by Dr Olivieri were non-existent or that the reservations which she had expressed had been dismissed.

98 Moreover, in any event, even if the applicant's professional reputation were to have been called into question in the contested decision, that would not have given her an interest in bringing proceedings to contest that decision, because Article 68 of Regulation No 2309/93 does not permit the Commission to take into account such matters in a decision to grant marketing authorisation (see, by analogy, *Norbrook Laboratories*, paragraphs 40 and 41).

99 Consequently, the applicant cannot claim that she has an interest in bringing proceedings in order to defend her professional reputation in the present case.

3. Conclusion

100 It follows from the foregoing that the applicant has not established an interest in bringing proceedings in order to protect public health or in order to defend her professional reputation. Consequently, since she has no interest in bringing proceedings to challenge the contested decision, her application must be declared inadmissible.

Costs

101 Under Article 87(2) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. Since the applicant has been unsuccessful, she must be ordered to bear her own costs and to pay those incurred by the Commission and the EMEA, including the costs relating to the interim proceedings.

102 Under the third subparagraph of Article 87(4), the Court may order an intervener to bear its own costs. Apotex shall therefore bear its own costs, both in the main proceedings and in the interim proceedings.

On those grounds,

THE COURT OF FIRST INSTANCE (Fifth Chamber)

hereby:

1. Dismisses the application as inadmissible;

2. Orders the applicant to bear her own costs and to pay those incurred by the Commission and the European Agency for the Evaluation of Medicinal Products, including those relating to the interim proceedings;

3. Orders the intervener to bear its own costs, both in the main proceedings and in the interim proceedings.

García-Valdecasas Lindh Cooke

Delivered in open court in Luxembourg on 18 December 2003.

H. Jung P. Lindh

Registrar President