JUDGMENT OF THE COURT OF FIRST INSTANCE (Second Chamber, Extended Composition)

28 January 2003 *

In Case T-147/00,

Les Laboratoires Servier, established in Neuilly-sur-Seine (France), represented by C. Norall, E. Wright, M.I.F. Utgès Manley, I.S. Forrester QC and J. Killick, lawyers, with an address for service in Luxembourg,

applicant,

v

Commission of the European Communities, represented by H. Støvlbæk and R. Wainwright, acting as Agents, with an address for service in Luxembourg,

defendant,

APPLICATION for annulment of the Commission decision of 9 March 2000 concerning the withdrawal of marketing authorisations of medicinal products for human use which contain the [following] substances: 'dexfenfluramine' and 'fenfluramine' (C(2000) 573),

* Language of the case: English.

THE COURT OF FIRST INSTANCE
OF THE EUROPEAN COMMUNITIES (Second Chamber, Extended Composition),

composed of: R.M. Moura Ramos, President, V. Tiili, J. Pirrung, P. Mengozzi and A.W.H. Meij, Judges,

Registrar: D. Christensen, Administrator,

having regard to the written procedure and further to the hearing on 7 and 8 May 2002,

gives the following

Judgment

Legal context

Directive 65/65/EEC

1 On 26 January 1965, the Council adopted Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (OJ, English Special Edition 1965-1966, p. 20). That directive has been amended on several occasions, in particular by

Council Directive 83/570/EEC of 26 October 1983 (OJ 1983 L 332, p. 1) and Council Directive 93/39/EEC of 14 June 1993 (OJ 1993 L 214, p. 22) (hereinafter, as amended, 'Directive 65/65'). Article 3 of that directive lays down the principle that no medicinal product may be placed on the market of a Member State unless an authorisation has first been issued by the competent authorities of that Member State in accordance with that directive or an authorisation has been granted in accordance with 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).

2 Article 4 of Directive 65/65 provides, *inter alia,* that, in order to obtain a marketing authorisation as provided for in Article 3, the person responsible for placing the product on the market must apply to the competent authority of the Member State concerned. Under Article 5, that authorisation is to be refused if it proves that the medicinal product is harmful in the normal conditions of use, or that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or that its qualitative and quantitative composition is not as declared, or if the particulars and documents submitted in support of the application do not comply with Article 4. Under Article 4b of Directive 65/65, when the marketing authorisation referred to in Article 3 is issued, the person responsible for placing that product on the market is to be informed, by the competent authorities of the Member State concerned, that they approve the summary of the product characteristics referred to in point 9 of the second paragraph of Article 4, the content of which is defined in Article 4a.

3 Article 10(1) of Directive 65/65 states that the authorisation is to be valid for five years and is to be renewable for five-year periods after consideration by the competent authority of a dossier containing, in particular, details of the data on pharmacovigilance and other information relevant to the monitoring of the medicinal product.

4 The first paragraph of Article 11 of Directive 65/65 provides:

'The competent authorities of the Member States shall suspend or revoke an authorisation to place a medicinal product on the market where that product proves to be harmful in the normal conditions of use, or where its therapeutic efficacy is lacking, or where its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is established that therapeutic results cannot be obtained with the medicinal product.'

5 Under Article 21 of Directive 65/65, a marketing authorisation for a medicinal product is not to be refused, suspended or revoked except on the grounds set out in that directive.

Directive 75/318/EEC

6 Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products (OJ 1975 L 147, p. 1), which has been amended on several occasions, in particular by Directives 83/570 and 93/39 (hereinafter, as amended, 'Directive 75/318'), lays down uniform rules for the conduct of the tests and trials referred to in point 8 of the second paragraph of Article 4 of Directive 65/65 and specifies the particulars which must accompany an application for marketing authorisation for a medicinal product pursuant to points 3, 4, 6 and 7 of that paragraph.

7 The seventh and eighth recitals in the preamble to that directive read as follows:

'[w]hereas the concepts of "harmfulness" and "therapeutic efficacy" referred to in Article 5 of Directive 65/65/EEC can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended; whereas the particulars and documents which must accompany an application for authorisation to place a medicinal product on the market [must] demonstrate that potential risks are outweighed by the therapeutic efficacy of the product; whereas failing such demonstration, the application must be rejected;

[w]hereas the evaluation of "harmfulness" and "therapeutic efficacy" may be modified in the light of new discoveries and standards and protocols must be amended periodically to take account of scientific progress'.

Directive 75/319/EEC

8 Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (OJ 1975 L 147, p. 13), amended on several occasions, in particular by Directives 83/570 and 93/39 (hereinafter, as amended, 'Directive 75/319'), establishes, in Chapter III (Articles 8 to 15c), a procedure for the mutual recognition of national marketing authorisations (Article 9), together with Community arbitration procedures.

9 That directive expressly provides for referrals to the Committee for Proprietary Medicinal Products (hereinafter 'the CPMP') of the European Agency for the

Evaluation of Medicinal Products, for application of the procedure governed by Article 13, where, in the context of the procedure for mutual recognition established by Article 9, a Member State considers that there are grounds for supposing that the authorisation of the medicinal product concerned may present a risk to public health and the Member States do not reach agreement within the prescribed time-limit (Article 10 of that directive), where Member States have adopted divergent decisions concerning the grant, suspension or withdrawal of national authorisations (Article 11), and in specific cases where the interests of the Community are involved (Article 12). In addition, the directive expressly provides that the variation, suspension and withdrawal of marketing authorisations granted in accordance with the provisions of Chapter III thereof are subject to the procedures laid down in Articles 13 and 14 (Articles 15 and 15a). Finally, Article 15b provides that Articles 15 and 15a are to apply by analogy to medicinal products authorised by the Member States following an opinion of the CPMP issued prior to 1 January 1995, in accordance with Article 4 of Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology (OJ 1987 L 15, p. 38). The procedures established by Articles 12 and 15a of Directive 75/319 are of particular relevance in the present case.

10 Article 12 of Directive 73/319 provides:

'The Member States or the Commission or the applicant or holder of the marketing authorisation may, in specific cases where the interests of the Community are involved, refer the matter to the [CPMP] for the application of the procedure laid down in Article 13 before reaching a decision on a request for a marketing authorisation or on the suspension or withdrawal of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary, in particular to take account of the information collected under the pharmacovigilance system provided for in Chapter Va.

The Member State concerned or the Commission shall clearly identify the question which is referred to the [CPMP] for consideration and shall inform the person responsible for placing the medicinal product on the market.

The Member States and the aforementioned person shall forward to the [CPMP] all available information relating to the matter in question.'

11 Article 15a of Directive 75/319 states:

'1. Where a Member State considers that the variation of the terms of a marketing authorisation which has been granted in accordance with the provisions of this chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the [CPMP] for the application of the [procedures] laid down in Articles 13 and 14.

2. Without prejudice to the provisions of Article 12, in exceptional cases, where urgent action is essential to protect public health, until a definitive decision is adopted a Member State may suspend the marketing and the use of the medicinal product concerned on its territory. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action.'

12 Article 13 of Directive 75/319 governs the procedure before the CPMP, which issues a reasoned opinion. Paragraph 5 of that article provides that the European Agency for the Evaluation of Medicinal Products is to forward the final opinion of the CPMP to the Member States, the Commission and the person responsible for placing the medicinal product on the market, together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions. Article 14 of that directive governs the Community decision-making procedure. The first subparagraph of Article 14(1) provides that within 30 days of the receipt of the CPMP opinion, the Commission is to prepare a draft of the decision to be taken in respect of the application, taking into account Community law. Under the third subparagraph of Article 14(1), '[w]here, exceptionally, the

draft decision is not in accordance with the opinion of the [European] Agency [for the Evaluation of Medicinal Products], the Commission shall also annex a detailed explanation of the reasons for the differences'. The final decision is adopted in accordance with the regulatory procedure governed by Articles 5 and 7 of Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission (OJ 1999 L 184, p. 23). The Commission is assisted in that procedure by the Standing Committee on Medicinal Products for Human Use, set up by Article 2b of Directive 75/318.

Community code on medicinal products for human use

13 All the directives relating to medicinal products for human use which govern the 'decentralised Community procedure', in particular Directives 65/65, 75/318 and 75/319, have been recast 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; hereinafter 'the Code'). Even though the Code was not in force when the contested decisions were adopted, it should be taken into account where appropriate. In so far as the Code restates in a more structured corpus, without amending them, the provisions of Directives 65/65 and 75/319, a systematic analysis of the provisions of Chapter III of Directive 75/319 is part of the scheme of that code.

Facts

14 The applicant, Les Laboratoires Servier, is the holder of marketing authorisations, originally issued by the competent national authorities, for medicinal products containing fenfluramine or dexfenfluramine, which are serotonergic anorectic agents. Those centrally-acting anorectics, so-called because they act at the level of the central nervous system, accelerate the feeling of satiety and are used in the treatment of obesity. In Europe, medicinal products containing

fenfluramine were first granted marketing authorisations in accordance with the provisions of Directive 65/65 in 1965, and medicinal products containing dexfenfluramine were first granted such authorisations in 1985. According to the information provided by the applicant, fenfluramine was approved in the United States in the 1970s, and dexfenfluramine in 1996.

15 Dexfenfluramine and fenfluramine have already been the subject of Commission Decision C(96) 3608 final/2 of 9 December 1996 concerning the placing on the market of the medicinal products for human use which contain the following substances: dexfenfluramine and fenfluramine (hereinafter 'the decision of 9 December 1996'), following a CPMP opinion under Article 12 of Directive 75/319 (see below, paragraphs 21 to 26).

16 After the Connolly Study (*New England Journal of Medicine* (NEJM) 1997, Vol. 337) had documented, and the United States Food and Drug Administration had publicised in July 1997 in an advisory notice entitled 'Health Advisory on Fenfluramine/Phentermine for Obesity', a series of cases of cardiac valve disorders (hereinafter 'CVDs'), reported in the United States and mainly concerning patients who had used fenfluramine in combination with phentermine, the applicant and its licensees immediately withdrew medicinal products containing fenfluramine or dexfenfluramine from the market pending further studies to check their safety.

17 In September 1997, in the light of those reported cases, the marketing authorisations of medicinal products containing dexfenfluramine or fenfluramine were suspended in all the Member States and in the United States.

18 Following a reassessment of those substances on the basis of Article 15a of Directive 75/319 by decision of 9 March 2000, the Commission ordered the

withdrawal of the marketing authorisations of medicinal products for human use which contain the following substances: 'dexfenfluramine' and 'fenfluramine' (Decision C(2000) 573; hereinafter 'the contested decision'). Annex I to that decision lists the medicinal products concerned, the undertakings which marketed them — namely the applicant, its subsidiaries or licensees —, and the Member States concerned.

19 According to the applicant's reply to a written question from the Court, the five-year validity period — specified in Article 10(1) of Directive 65/65 — of the marketing authorisations of some of the medicinal products marketed by the applicant and covered by the contested decision had expired before that decision was adopted. At the hearing, the applicant explained, however, that when that decision was adopted those authorisations were the subject of renewal procedures before the competent authorities of the Member States concerned. Those procedures were suspended following the contested decision. The marketing authorisations therefore remained in force, in accordance with the applicable national rules, pending the adoption of decisions on the applications for renewal. The Commission has not contested the applicant's submissions in that regard.

20 At the hearing, the applicant did however add that, in the meantime, the competent authorities of the Member States concerned had either suspended the marketing authorisations of the medicinal products in question or withdrawn them in compliance with the contested decision.

Commission Decision C(96) 3608 final/2 of 9 December 1996

21 On 17 May 1995, the Federal Republic of Germany made a referral to the CPMP, under Article 12 of Directive 75/319, expressing its concerns in respect of the risks presented by certain centrally-acting anorectics, including the medicinal

products containing serotonergic substances marketed by the applicant, as well as 'amphetamine-like' anorectics. While the latter enhance neurotransmission at the level of the neurotransmitters (catecholamine) and usually have a stimulant effect, serotonergic anorectics act by increasing the release and reducing the re-uptake of serotonin and have no stimulant or euphoriant effect. The competent German authority suspected all those medicinal products of inducing primary pulmonary hypertension (hereinafter 'PPH').

22 The CPMP initiated the procedure provided for in Article 13 of Directive 75/319 for the purpose of investigating those two classes of anorectics.

23 In his scientific assessment report of 5 February 1996, the rapporteur, Dr Le Courtois, assessed the benefit/risk balance of anorectics. In that connection, he found, first, that there was a risk of PPH, which was 'most of the time fatal', a finding which was based on the report of 7 March 1995 of the International Primary Pulmonary Hypertension Study (hereinafter 'the IPPH Study'). Second, he observed: 'when obesity is [so] marked that it decreases the patient's life expectancy, there is a need for a pharmacological treatment as adjunctive therapy, in the context of a global approach including diet, psychotherapy, exercise. Only anorectics are today available as pharmacological treatment, thus they have a place in the treatment of obesity'. As regards, more specifically, fenfluramine and dexfenfluramine, he found that they satisfied the criterion of long-term efficacy (one year) and complied with the aim of the treatment of obesity, which is prolonged and lasting weight-loss. The lack of dependence associated with the use of those substances facilitated their long-term use. However, the rapporteur found that there was a strong association between PPH and those substances. Moreover, even if fenfluramine and dexfenfluramine appeared to be the most effective substances, it had not yet been established that their use led to a reduction in morbidity and mortality. The rapporteur concluded by recommending the harmonisation of certain information contained in the summaries of product characteristics of the medicinal products in question.

24 On 17 July 1996, the CPMP issued a final opinion on fenfluramine and dexfenfluramine. It recommended maintaining the marketing authorisations subject to a certain number of amendments to the summaries of product characteristics of medicinal products containing those substances.

25 In its assessment report of 18 July 1996 on all anorectic agents, the CPMP noted that, according to the conclusions of the 'pharmacovigilance' working party, which is composed of national agents in the field of pharmacovigilance and is responsible for advising the CPMP on matters relating to the safety of medicinal products, the report of 7 March 1995 of the IPPH Study had established a causal link between the use of anorectic agents and the occurrence of PPH. The documents before the Court show that that study was carried out between 1992 and 1994, at the applicant's initiative, by an international group of independent experts in epidemiology and pneumology, and its aim was to assess the likelihood of a relationship between the incidence of PPH and exposure to a range of factors, especially the use of anorectics. The CPMP also noted, in particular, that cases of PPH had been reported in association with all the centrally-acting anorectics (with the exception of fenbutrazate and propylhexedrine). It stated that this was 'a class effect'. As regards, more specifically, fenfluramine and dexfenfluramine, it stated that those substances had recently been the subject of short and long-term studies, as well as of reports and numerous publications. Their long-term efficacy had been proven. That efficacy had, however, only been demonstrated with regard to weight-loss. In those circumstances, the CPMP considered the benefit/risk balance of the anorectic agents to be favourable, subject to amendment of the summaries of product characteristics of the medicinal products in question.

26 That procedure led to the adoption of the decision of 9 December 1996 which is expressly based on Articles 12 and 14 of Directive 75/319. In line with the CPMP opinion of 17 July 1996, the Commission instructed the Member States

concerned to amend certain clinical particulars in the summaries of product characteristics approved when the marketing authorisations of the medicinal products in question were granted. It stipulated that the following clinical particulars be included:

'Therapeutic indications

Adjunctive therapy to diet, in patients with obesity and a body mass index (BMI) of 30 kg/m^2 or higher who have not responded to an appropriate weight-reducing regimen alone.

Note: a recently conducted, controlled, double-blind study lasting one year demonstrated a two-fold increase in the number of responders at one year when dexfenfluramine or fenfluramine was combined with a low-calorie diet in comparison with a diet alone. A 10% reduction in the initial body weight was observed in 35% and 17% of patients, respectively. Efficacy has only been demonstrated with regard to weight reduction. No significant data on change in morbidity or mortality are yet available.'

'Posology and method of administration

It is recommended that treatment should be conducted under the care of physicians experienced in the treatment of obesity....

The management of obesity should be undertaken using a global approach, and should include dietary, medical and psychotherapeutic methods....

Treatment should only be continued beyond three months in patients who have responded to treatment as indicated by a weight-loss greater than or equal to 10% of the initial weight within three months of the start of treatment. Unless weight-loss is maintained, treatment should not be continued. No data regarding efficacy of these agents are available beyond one year of treatment.'

'Contraindications

— Pulmonary artery hypertension

— Current or past medical history of cardio-vascular or cerebro-vascular disease

— Current or past medical history of psychiatric disorders including anorexia nervosa and depression

— Propensity towards drug abuse, known alcoholism

— Children below 12 years

Combination drug therapy with any other centrally-acting anorectic agent is contraindicated due to the increased risk of potentially fatal pulmonary artery hypertension.'

'Special warnings and precautions for use

... Cases of severe, often fatal, pulmonary artery hypertension have been reported in patients who have received anorectics of [this] type... An epidemiological study has shown that dexfenfluramine or fenfluramine intake is a risk factor involved in the development of pulmonary artery hypertension and that the use of anorectics is strongly associated with an increased risk for this adverse drug reaction. In view of this rare but serious risk, it must be emphasised that: careful compliance with the indication and the duration of treatment is required; a duration of treatment greater than three months and a BMI [greater than or equal to] 30kg/m^2 increase the risk of pulmonary artery hypertension; the onset or aggravation of exertional dyspnea suggests the possibility of occurrence of pulmonary artery hypertension. Under these circumstances treatment should be immediately discontinued and the patient referred to a specialist unit for investigation.'

Finally, the undesirable effects referred to in the decision of 9 December 1996 included PPH, certain effects on the central nervous system (mainly depression, confusion, agitation, sleep disorders, dizziness and vertigo) and cardio-vascular effects (mainly tachycardia and syncope).

The contested decision

27 On 22 October 1997, after several Member States had notified the European Agency for the Evaluation of Medicinal Products of their decisions to suspend the marketing authorisations of medicinal products containing dexfenfluramine or fenfluramine (see above, paragraph 17), the matter was referred to the CPMP under Article 15a of Directive 75/319.

28 The report and supplementary report ('the Picon/Abadie Report' and 'the Castot/Costagliola/Fosset-Martinetti/Ropers Report') were submitted in June 1998 and April 1999 respectively. On 22 April 1999, the CPMP gave its first opinion on the scientific assessment of medicinal products containing dexfenfluramine or fenfluramine, in which it recommended withdrawal of the marketing authorisations of those medicinal products.

29 On 11 May 1999, the applicant brought an appeal before the CPMP against that opinion, pursuant to the second sentence of Article 13(4) of Directive 75/319. Reports were submitted by the rapporteur ('the O'Mahony/Slattery Report' of 19 July 1999, updated on 20 August 1999) and the co-rapporteur ('the Van Bronswijk Report' of 16 July 1999) appointed for that appeal procedure.

30 In its final opinion of 31 August 1999 on medicinal products containing dexfenfluramine or fenfluramine, the CPMP rejected the applicant's appeal and upheld its recommendation that the marketing authorisations for the medicinal products in question be withdrawn, on the ground that they had an unfavourable benefit/risk balance.

31 In its scientific conclusions annexed to that opinion, and also in its assessment report on dexfenfluramine and fenfluramine of 31 August 1999, the CPMP stated that the two main safety concerns which it had examined were PPH and CVDs 'under normal conditions of use'.

32 As regards PPH, the CPMP relied, first, on observations based on 105 spontaneously reported cases of PPH, recorded in reports received prior to 31 December 1998 and, second, on the IPPH Study. It referred to the report of

7 March 1995 of that study, published in the *New England Journal of Medicine* of 29 August 1996 (NEJM, Vol. 335, No 9), and to results restricted to fenfluramine derivatives reported in specialist correspondence (NEJM of 11 February 1999, Vol. 340, No 6). After 'reassess[ing] the IPPH Study in [the] light of the arguments' of the marketing authorisation holders concerned, it concluded that 'the strong evidence from [that] study for a causal association between anorectic agents and PPH remains' valid.

33 As regards CVDs, the CPMP observed that, in the spontaneously reported cases of CVDs, the patients had generally been treated with a combination of anorectic agents for a median duration of five months at the time of diagnosis. The case reports showed that the CVDs were potentially severe, sometimes requiring surgery. There were no definitive data concerning the clinical course (worsening or regression) of those CVDs. The epidemiological studies, in particular those by Jick, Weissman and Khan (NEJM of 10 September 1998, Vol. 339, No 11), showed, *inter alia*, that: (1) the most convincing comparative studies point towards the reality of the association between dexfenfluramine and fenfluramine and the occurrence of CVDs; (2) that association is likely to be of a causal nature, this being supported by effects dependent on dose and treatment duration, as suggested in some studies; (3) the increase in the prevalence of CVDs (which reflects the number of patients affected by the disorder and its duration) could be slight when the treatment duration is short, for example less than three months: those results might explain the low number of reports in Europe; (4) that association exists for dexfenfluramine or fenfluramine administered alone. It is not clear whether combination therapy with other anorectic agents increases the risk. Some data support that hypothesis but are difficult to interpret given the longer treatment duration where combination therapy is used. The CPMP therefore concluded that '[a]lthough a mechanism for causality has not been determined and despite the wide variations in reporting frequencies for spontaneous reports of [CVDs] associated with the use of dexfenfluramine and fenfluramine... the data from spontaneous reports and from the large number of epidemiological studies indicate that there is a risk of [CVDs] occurring in patients treated with dexfenfluramine and fenfluramine'.

34 As regards efficacy, the CPMP observed that: (1) the mean effect of the substances examined was modest, never exceeding 3 to 4 kg of weight-loss whatever the duration. However, in the one-year INDEX study with dexfenfluramine, the percentage of responders, that is to say those patients losing at least 10% of their initial weight, was almost twice as high as in the placebo group; (2) the maintenance of a long-term weight-loss was demonstrated for treatment with dexfenfluramine or fenfluramine lasting one year; (3) the weight-loss did not produce a change in fat distribution, which is a recognised cardiovascular risk factor; (4) the effects on metabolic risk factors were no more than would be expected as a result of the weight-loss and could not be attributed to dexfenfluramine or fenfluramine alone; (5) weight-regain was observed as soon as treatment was stopped. The CPMP concluded:

'[t]he objective of treating obesity is to reach a clinically relevant and maintained weight-loss, [likely] to decrease cardiovascular and other recognised risk factors and their related morbidity and mortality. Such an objective can only be reached through long-term treatment. This is based on accumulated scientific knowledge acquired over the years and is laid down in current medical recommendations. So the limited therapeutic efficacy of dexfenfluramine and fenfluramine has to be assessed in view of their safety profiles'.

35 Weighing that 'limited' therapeutic efficacy against 'the well-known risk of [PPH] which has been fully taken into account in the Decision... of 9 December 1996' and the fact that 'pharmacoepidemiological evidence and spontaneous reports provide evidence supporting [a finding] that dexfenfluramine and fenfluramine are associated with the occurrence of [CVDs], mainly aortic valve disorders', the CPMP considered the benefit/risk balance of those substances to be unfavourable and recommended withdrawing the marketing authorisations of all the medicinal products containing those substances.

36 On 9 March 2000, the Commission adopted the contested decision. In Article 1 of the operative part of that decision, the Commission ordered the Member States to withdraw 'the national marketing authorisations provided for in the first paragraph of Article 3 of Directive 65/65/EEC concerning the medicinal products [containing dexfenfluramine and fenfluramine] listed in Annex I' to that decision. Article 2 of that decision justified that withdrawal by referring to the scientific conclusions which were appended to the CPMP final opinion of 31 August 1999 on those substances (Annex II). Article 3 of the decision required the Member States concerned to comply with the contested decision within 30 days of its notification.

Procedure and forms of order sought

37 By application lodged at the Court Registry on 31 May 2000, the applicant brought the present action.

38 By decision of 14 March 2002, the Court referred the case to the Second Chamber, Extended Composition, pursuant to Article 51(1) of the Rules of Procedure of the Court of First Instance.

39 By order of 25 April 2002, the President of the Second Chamber, Extended Composition, after hearing all the parties, ordered that for the purposes of the oral procedure the present case be joined with Joined Cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00.

40 Upon hearing the report of the Judge-Rapporteur, the Court of First Instance (Second Chamber, Extended Composition) opened the oral procedure. By way of measures of organisation of procedure, the parties were requested to produce certain documents and to reply to a number of written questions from the Court. They complied with those requests.

41 The oral arguments of the parties were heard as were their replies to the questions put by the Court at the hearing on 7 and 8 May 2002. At that hearing, the experts advising the parties were also heard, *inter alia* at the request of the parties.

42 The applicant claims that the Court should:

— annul the contested decision;

— order the defendant to pay the costs.

43 The defendant contends that the Court should:

— dismiss the application;

— order the applicant to pay the costs.

Law

44 The applicant bases its case on, first, breach of Article 11 of Directive 65/65; second, procedural irregularity of the CPMP opinion; third, manifest error of assessment and failure to observe the principle of sound administration; fourth, failure to observe the principle of proportionality and, fifth, failure to state adequate reasons for the contested decision.

45 As a preliminary point, it should be noted that, according to well-established case-law, the lack of competence of the institution which has adopted the contested measure constitutes a ground for annulment for reasons of public policy, which must be raised by the Community judicature of its own motion even though none of the parties has asked it to do so (see, to that effect, Case 19/58 *Germany* v *High Authority* [1960] ECR 225, 233, and Case C-210/98 P *Salzgitter* v *Commission* [2000] ECR I-5843, paragraph 56).

46 In the present case, the Court must therefore examine of its own motion whether the Commission was competent to take the contested decision.

47 In the light of its judgment in Joined Cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00 *Artegodan and Others* v *Commission* [2002] ECR II-4945, the Court nevertheless considers it necessary first to provide some general information on the application of the criteria for withdrawal of marketing authorisations of medicinal products, set out in Article 11 of Directive 65/65, in view of the pleas raised by the applicant in disputing the proper foundation of the contested decision.

General observations regarding the criteria for withdrawal of marketing authorisations of medicinal products applied in the present case

48 First of all, the applicant disputes the assessment of the benefit/risk balance of the substances in question when the criteria for withdrawal of marketing authorisations set out in Article 11 of Directive 65/65 were applied in the present case.

49 In that regard, it is sufficient to note that, in any evaluation of a medicinal product, the degree of harmfulness which the competent authority may regard as acceptable depends, in practical terms, on the benefits which the medicinal product is deemed to provide and, consequently, the criteria of the efficacy and the safety of a medicinal product, set out in Article 11 of Directive 65/65, can only be examined in relation to each other (*Artegodan and Others* v *Commission*, cited above, paragraph 178).

50 The other complaints raised by the applicant relate more specifically to the evaluation, when applying the safety criterion, of the risk of PPH — which had already been taken into consideration in the decision of 9 December 1996 (see above, paragraphs 22 to 26) — and of the new risk of CVDs, allegedly associated with the use of the substances in question. The applicant particularly criticises the inconsistency and inadequacy of the reasons given in the CPMP final opinion of 31 August 1999, in the light of the scientific studies taken into consideration by that committee. It submits that those studies do not prove the existence of a causal link between use of the substances in question and occurrence of the medical disorders referred to above. Moreover, some of those studies were not sufficiently scientifically rigorous. The applicant also claims that by endorsing that opinion in the contested decision the Commission made a manifest error of assessment and failed to observe the principle of sound administration. Furthermore, in requiring the withdrawal of the marketing authorisations of the medicinal products in question, the Commission failed to observe the principle of proportionality given, first, the efficacy and safety of those medicinal products and, second, their withdrawal from the market on the

applicant's initiative pending the results of further tests which the applicant was planning to carry out in order to verify their safety. Finally, the contested decision did not state adequate reasons, inasmuch as the Commission failed to justify the adoption of a decision which was fundamentally different from the decision of 9 December 1996.

51 As regards the complaints referred to in the preceding paragraph, it should be observed even at this stage that it is evident from the CPMP's scientific conclusions justifying the contested decision (see above, paragraphs 31 to 36), as well as from the background to the dispute, that that decision relies on the demonstration, on the basis of new scientific data, of a risk of CVDs, allegedly associated with the substances in question. As the Commission indeed expressly confirmed in its pleadings and at the hearing, it was the taking into consideration of that new risk, as compared with the evidence available when the same substances were evaluated in 1996, which led the CPMP, in its opinion of 31 August 1999, and the Commission, in the contested decision, to alter the favourable assessment of the benefit/risk balance of the substances in question which they had made in 1996. On that point, it should be noted that the information concerning the 'limited' efficacy of the substances under consideration, which was provided in the CPMP's scientific conclusions annexed to the contested decision, does not include any assessment of the efficacy of those substances which differs from that made in 1996, on the basis of the same scientific studies as to that efficacy.

52 Against that background, it will be for the competent national authorities, where appropriate, to carry out a new assessment of the benefit/risk balance of the substances in question, after having evaluated in particular the risks, *inter alia* of CVDs, associated with those substances, in the light of the most up-to-date scientific data available at the time of that assessment. If they find that there are new data — as compared with the last assessment of the medicinal products in question, which in this case was made when the decision of 9 December 1996 was adopted — which, while not resolving the scientific uncertainty, may raise reasonable doubts as to the safety and/or efficacy of those medicinal products and lead to an unfavourable assessment of their benefit/risk balance, the competent authorities are obliged, under Article 11 of Directive 65/65, interpreted in accordance with the precautionary principle, which is a general principle of

Community law, to suspend or withdraw the marketing authorisations of those medicinal products (*Artegodan and Others* v *Commission*, in particular paragraphs 172, 184, 192 and 194).

The Commission's competence to take the contested decision

53 The Court must determine whether the national marketing authorisations of the medicinal products in question fell — following their amendment by the decision of 9 December 1996, based on Article 12 of Directive 75/319 (see above, paragraph 26) — within the scope of Article 15a(1) of that directive, on which the contested decision is based. That question arises in exactly the same terms as the question of the Commission's competence to adopt the contested decisions in Joined Cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00 *Artegodan and Others* v *Commission*, cited above, which were joined with the present case for the purposes of the oral procedure. By requiring, in this case, substantial amendments to the clinical particulars included in the summaries of product characteristics of the marketing authorisations of the serotonergic anorectic agents in question, the Commission harmonised those authorisations in the decision of 9 December 1996, inasmuch as the summary of product characteristics, approved when a marketing authorisation is granted for a medicinal product, is the essential aspect of that authorisation. Similarly, the national marketing authorisations of medicinal products containing amphetamine-like anorectics, considered in the cases giving rise to the judgment in *Artegodan and Others* v *Commission*, were harmonised by Commission Decision C(96) 3608 final/1 of 9 December 1996, based on Article 12 of Directive 75/319, before becoming the subject of the decisions at issue in those cases, which were adopted by the Commission under Article 15a(1) of that directive.

54 Against that background, the Commission was given an opportunity at the hearing to explain its reasoning with respect to the authority with competence to withdraw the marketing authorisations of the medicinal products in question. In addition, in the nine cases joined for the purposes of the oral procedure, the

parties received an advance written request from the Court to express at the hearing their views on the consequences, if any, of a possible annulment of the contested decisions on the ground of the Commission's lack of competence.

55 At the hearing, the applicant merely stated that in the event of such an annulment of the contested decision the medicinal products in question would not automatically be placed back on the market. That step would depend on the results of the study which it plans to carry out to demonstrate the efficacy and safety of those medicinal products, if the contested decision is annulled by the Court.

56 For its part, the Commission considers that Article 15a(1) of Directive 75/319, which expressly refers to authorisations granted in accordance with the provisions of Chapter III, also applies to marketing authorisations harmonised under Article 12 of that directive.

57 That argument must be rejected for the same reasons, to which reference is made, as those which led to the Court's finding that the Commission did not have competence to adopt the contested decisions in *Artegodan and Others* v *Commission*, since, in this matter, the questions of law and of fact at issue are the same, as has been pointed out above (see paragraph 53).

58 In the present case, it is therefore sufficient to find, first, that in the scheme of Chapter III of Directive 75/319, leaving aside the decision of 9 December 1996, the management of the purely national marketing authorisations of the medicinal products in question came within the residual field of exclusive competence of the Member States concerned (*Artegodan and Others* v *Commission*, paragraphs 114 to 116).

59 Moreover, it is clear from the very wording of Article 12 of Directive 75/319 that that article establishes in the field of competence of the Member States a purely consultative procedure, which is also optional and can, moreover, be initiated not only by the Member States concerned, but also by the Commission, or the applicant or holder of a marketing authorisation. In addition, in the system established by Chapter III of Directive 75/319, that article, which is not one of the provisions more specifically providing the framework for the mutual recognition procedure, cannot be interpreted in the light of the particular objective of that procedure, which is intended ultimately to bring about the adoption of a common decision by the Member States concerned, where necessary by way of the Community arbitration procedure established by Article 10 of that directive if the Member States fail to reach agreement within the prescribed time-limit (*Artegodan and Others* v *Commission*, paragraphs 132 and 133).

60 In the scheme of Chapter III of Directive 75/319, Article 12 of that directive is intended to apply in the residual field of exclusive competence of the Member States, or when the initial marketing authorisation of a medicinal product is granted by the reference Member State. Within that legal framework, the Member States, which have merely an option to consult the CPMP, cannot find themselves by implication deprived of their competence if they make use of that option or if the Commission, the applicant, or the holder of a marketing authorisation makes a referral to the CPMP under Article 12. In the field of the mutual recognition procedure, such a removal of competence would however, if a matter were referred to the CPMP under Article 12 by the reference Member State, lead to the immediate application of a Community arbitration procedure and the circumvention of the preliminary stages of mutual recognition and concertation between the Member States concerned with a view to reaching an agreement — on the basis of all the documents and information referred to in Article 4 of Directive 65/65 —, stages which are expressly provided for by Articles 9(4) and 10(2) of Directive 75/319. In the field of the exclusive competence of the Member States, that removal of competence would also lead to the immediate application of an arbitration procedure, in respect of medicinal

products which have never been the subject of a preliminary joint examination by the Member States concerned, similar to that which distinguishes the mutual recognition procedure (*Artegodan and Others* v *Commission,* paragraphs 129, 130 and 142).

61 Against that background, in the absence of an express provision, the principle set out in the first paragraph of Article 5 EC that the Community is to act within the limits of the powers conferred upon it, precludes an interpretation of Article 12 of Directive 75/319 to the effect that it implicitly empowers the Commission to adopt a binding decision under the procedure provided for in Article 14 of that directive (*Artegodan and Others* v *Commission,* paragraphs 136 to 147).

62 Second, the principle that the Community can only act within the powers conferred on it also militates against an interpretation of Article 15a(1) of Directive 75/319 to the effect that, in the absence of any provision providing for such a transfer of competence, the optional harmonisation of certain marketing authorisations, in accordance with a non-binding opinion of the CPMP under Article 12 of that directive, has the effect of depriving the Member States concerned of their competence in respect of subsequent decisions on the amendment, suspension or withdrawal of those authorisations. In the present case, the notion that such achieved harmonisation must be maintained — which would find its concrete expression in the implementation of a Community arbitration procedure — is not apparent from either the provisions of Chapter III of Directive 75/319 or the aim pursued by that chapter (*Artegodan and Others* v *Commission,* paragraphs 149 to 154).

63 In those circumstances, in the system of harmonisation set up by Chapter III of Directive 75/319, which is based specifically on the principle of mutual recognition in association with Community arbitration procedures, the concept of a marketing authorisation granted in accordance with the provisions of that chapter, referred to in Article 15a(1), covers only authorisations granted by way of mutual recognition or arbitration. That concept cannot be interpreted as also including national authorisations harmonised following optional consultation of

the CPMP under Article 12, which therefore remain within the essentially residual field of exclusive competence of the Member States concerned (*Artegodan and Others* v *Commission,* paragraphs 149 and 155).

64 It follows that, in the present case, although the marketing authorisations of the medicinal products in question were harmonised by the decision of 9 December 1996, which has no legal basis but is no longer open to challenge, they do not come within the scope of Article 15a(1) of Directive 75/319.

65 The contested decision, which was adopted under that article, is therefore also without legal basis.

66 For all those reasons, the contested decision must be annulled, and there is no need to examine the other pleas.

Costs

67 Under Article 87(2) of the Rules of Procedure of the Court of First Instance, 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 defendant has been unsuccessful, it must, in accordance with the form of order sought by the applicant, be ordered to pay all the costs.

On those grounds,

THE COURT OF FIRST INSTANCE
(Second Chamber, Extended Composition),

hereby:

1. Annuls the Commission Decision of 9 March 2000 (C(2000) 573);

2. Orders the Commission to pay all the costs.

Moura Ramos Tiili

Pirrung Mengozzi Meij

Delivered in open court in Luxembourg on 28 January 2003.

H. Jung R.M. Moura Ramos

Registrar President