JUDGMENT OF THE COURT OF FIRST INSTANCE

(Second Chamber, Extended Composition)

26 November 2002

Case T-76/00

(Medicinal products for human use - Community arbitration procedures - Withdrawal of marketing authorisations - Competence - Criteria for withdrawal - Anorectics: amfepramone, clobenzorex, fenproporex, norpseudoephedrine, phentermine - Directives 65/65/EEC and 75/319/EEC)

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 GmbH, established in Lüchow (Germany), represented by U. Doepner, lawyer, with an address for service in Luxembourg,

applicant in Case T-74/00,

Bruno Farmaceutici SpA, established in Rome (Italy),

Essential Nutrition Ltd, established in Brough (United Kingdom),

Hoechst Marion Roussel Ltd, established in Denham (United Kingdom),

Hoechst Marion Roussel SA, established in Brussels (Belgium),

Marion Merell SA, established in Puteaux (France),

Marion Merell SA, established in Barcelona (Spain),

Sanova Pharma GmbH, established in Vienna (Austria),

Temmler Pharma GmbH & Co. KG, established in Marburg (Germany),

represented by B. Sträter and M. Ambrosius, lawyers, with an address for service in Luxembourg,

applicants in Case T-76/00,

Schuck GmbH, established in Schwaig (Germany), represented by B. Sträter and M. Ambrosius, lawyers, with an address for service in Luxembourg,

applicant in Case T-83/00,

Laboratórios Roussel L^da^, established in Mem Martins (Portugal), represented by B. Sträter and M. Ambrosius, lawyers, with an address for service in Luxembourg,

applicant in Cases T-84/00 and T-85/00,

Laboratoires Roussel Diamant SARL, established in Puteaux (France), represented by B. Sträter and M. Ambrosius, lawyers, with an address for service in Luxembourg,

applicant in Case T-84/00,

Roussel Iberica SA, established in Barcelona (Spain), represented by B. Sträter and M. Ambrosius, lawyers, with an address for service in Luxembourg,

applicant in Case T-85/00,

Gerot Pharmazeutika GmbH, established in Vienna (Austria), represented by K. Grigkar, lawyer, with an address for service in Luxembourg,

applicant in Case T-132/00,

Cambridge Healthcare Supplies Ltd, established in Norfolk (United Kingdom), represented by D. Vaughan, K. Bacon, barristers, and S. Davis, solicitor, with an address for service in Luxembourg,

applicant in Case T-137/00,

Laboratoires pharmaceutiques Trenker SA, established in Brussels, represented by L. Defalque and X. Leurquin, lawyers, with an address for service in Luxembourg,

applicant in Case T-141/00,

v

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

defendant,

APPLICATION for annulment of the Commission decisions of 9 March 2000 concerning the withdrawal of marketing authorisations of medicinal products for human use containing respectively □amfepramone□ (C(2000) 453), as regards Cases T-74/00, T-76/00 and T-141/00, *inter alia* □norpseudoephedrine□, □clobenzorex□ and □fenproporex□ (C(2000)

608), as regards Cases T-83/00 to T-85/00, and ‘phentermine’ (C(2000) 452), as regards Cases T-132/00 and T-137/00,

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 is to 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 applicants are holders of marketing authorisations, initially issued by the competent national authorities, for medicinal products containing ‘amphetamine-like’ 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 have been used for many years in a number of Member States in the treatment of obesity.

15.

The applicants in Cases T-74/00, T-76/00 and T-141/00 are holders of marketing authorisations of medicinal products containing amfepramone. The applicants in Cases T-83/00, T-84/00 and T-85/00 hold marketing authorisations for medicinal products containing norpseudoephedrine, clobenzorex and fenproporex respectively. The applicants in Cases T-132/00 and T-137/00 hold marketing authorisations for medicinal products containing phentermine.

16.

On 9 March 2000, the Commission adopted, on the basis of Article 15a of Directive 75/319, three decisions (hereinafter ‘the contested decisions’) concerning the withdrawal of marketing authorisations of medicinal products for human use which contain ‘phentermine’ (C(2000) 452), ‘amfepramone’ (C(2000) 453) and the substances ‘clobenzorex’, ‘fenbutrazate’, ‘fenproporex’, ‘mazindol’, ‘mefenorex’, ‘norpseudoephedrine’, ‘phenmetrazine’, ‘phendimetrazine’ or ‘propylhexedrine’ (C(2000) 608). In Article 1 of the operative part of each of those decisions, 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 … concerning the medicinal products listed in Annex I [to the decision] which contain the [substance or substances assessed]’. Article 2 of each of the contested decisions justified that withdrawal by referring to the scientific

conclusions which were appended to the CPMP final opinion of 31 August 1999 on the substance or substances concerned and annexed to the respective decision (Annex II). Article 3 of each of those decisions required the Member States concerned to comply with the decision within 30 days of its notification.

17.

The anorectic agents referred to in those decisions had already been the subject of Commission Decision C(96) 3608 final/1 of 9 December 1996 concerning the placing on the market of the medicinal products for human use which contain the following substances: clobenzorex, norpseudoephedrine, phentermine, fenproporex, mazindol, amfepramone, phendimetrazine, phenmetrazine, mefenorex (hereinafter "the decision of 9 December 1996"), subsequent to an opinion of the CPMP to which the matter had been referred under Article 12 of Directive 75/319 (see below, paragraphs 20 to 25). The contested decisions were adopted following a reassessment of those substances, under Article 15a of that directive, at the request of several Member States.

18.

According to the applicants' replies 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 which are marketed by the applicants and covered by the contested decisions, had expired before those decisions were adopted. However, the applicants explained at the hearing that when those decisions were 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 decisions. 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 applicants' submissions in that regard.

19.

At the hearing, the applicants did however add that, in the meantime, the competent authorities of the Member States concerned have either suspended the marketing authorisations of the medicinal products in question or withdrawn them in compliance with the contested decisions. In reply to a question put by the Court, the applicants confirmed that if the contested decisions were annulled on the ground of the Commission's lack of competence, the resumption, if any, of the marketing of the medicinal products in question would be conditional upon the adoption of positive decisions by the competent national authorities.

Commission Decision C(96) 3608 final/1 of 9 December 1996

20.

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. That referral covered both "amphetamine-like" anorectics - marketed by the applicants -, which enhance neurotransmission at the level of the neurotransmitters (catecholamine) and usually have a stimulant effect, and serotonergic anorectics, which act by increasing the release and reducing the re-uptake of serotonin and have no stimulant or euphoriant effect. The competent national authority suspected those medicinal products of inducing primary pulmonary hypertension ("PPH").

21.

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

22.

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", and that anorectics in combination with diet induced a weight-loss of 3 to 4 kg and were "often prescribed in an aesthetic aim to young women who are not really obese". He inferred that measures restricting the use of anorectics were justified because, in the absence of such measures, "the risks linked with the use of anorectics obviously outweigh the therapeutic benefit". Second, he pointed out that "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". He concluded by recommending the harmonisation of certain information contained in the summaries of product characteristics of the medicinal products in question.

23.

On 17 July 1996, the CPMP issued three final opinions on amfepramone, phentermine and the third group of "amphetamine-like" substances under consideration, which included clobenzorex, fenproporex and norpseudoephedrine. It recommended maintaining the marketing authorisations subject to a certain number of amendments to the summaries of product characteristics for the medicinal products containing those substances.

24.

In its assessment report of 18 July 1996 on all anorectic agents, the CPMP essentially explained *inter alia* that the International Primary Pulmonary Hypertension Study (hereinafter "the IPPH Study"), which had been the subject of a report of 7 March 1995, had proven a causal link between the use of anorectics and the occurrence of PPH. The risk of PPH was higher when the treatment duration exceeded three months. The CPMP noted that the reported cases showed that this was "a class effect" common to all anorectics. As regards the efficacy of those substances, the CPMP found that the weight-loss obtained after short-term treatment was 2 to 5 kg on average, that long-term efficacy had not been established, and that weight-regain occurred immediately after the pharmacological treatment was discontinued. In those circumstances, it considered the benefit/risk balance for the anorectic compounds to be favourable, subject to amendment of the summaries of product characteristics for the medicinal products in question.

25.

That procedure led to the adoption of the decision of 9 December 1996 which is expressly based on Article 14 of Directive 75/319. In line with the CPMP opinions 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/m² or higher who have not responded to an appropriate weight-reducing regimen alone.

Note: short-term efficacy only has been demonstrated with regard to weight-reduction. No significant data on changes 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 which should include dietary, medical and psychotherapeutic methods. ...

The duration of treatment is 4-6 weeks and should not exceed three months.

Contraindications

- Pulmonary artery hypertension
- Severe arterial hypertension
- Current or past 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 anorectic intake is ... strongly associated with an increased risk for this adverse drug reaction. In view of this rare but serious risk ... careful compliance with the indication and the duration of treatment is required ... .

Undesirable effects

... pulmonary arterial hypertension ... The occurrence or aggravation of exertional dyspnea is usually the first clinical sign and requires treatment discontinuation and investigation in a specialised unit ... .

[E]ffects [on the central nervous system]

- the prolonged use of [these substances] is associated with a risk of pharmacological tolerance [reduction in efficacy], dependence and withdrawal syndrome
- the most common adverse reactions which have been described are: psychotic reactions or psychosis, depression, nervousness, agitation, sleep disorders and vertigo
- convulsions have been reported

Cardio-vascular effects

- the most common reported reactions are tachycardia, palpitations, hypertension, precordial pain

- rarely cases of cardiovascular or cerebro-vascular accidents have been described in patients treated with anorectic agents. In particular stroke, angina, myocardial infarction, cardiac failure and cardiac arrest have been reported.

Decision C(2000) 453 concerning the withdrawal of marketing authorisations of medicinal products which contain amfepramone, contested in Cases T-74/00, T-76/00 and T-141/00

26.

By letter of 7 November 1997, the Belgian Ministry for Social Affairs, Public Health and the Environment informed the CPMP of several cases of cardiac valve disorders observed in patients treated with medicinal products containing fenfluramine, either in monotherapy or in combination with medicinal products containing phentermine and amfepramone. The procedure under Article 15a of Directive 75/319 had already been initiated, on 22 October 1997, in respect of fenfluramine and dexfenfluramine. The Belgian Government therefore requested that such a procedure be initiated in respect of amfepramone and phentermine.

27.

On 19 November 1997, the CPMP initiated the procedure under Article 13 of Directive 75/319 in respect of amfepramone used in monotherapy.

28.

From 12 to 14 May 1998, the draft first scientific report on amfepramone (the Picon/Abadie Report) was discussed by the pharmacovigilance working party, which is composed of national experts in the field of pharmacovigilance and is responsible for advising the CPMP on matters relating to the safety of medicinal products (pharmacological vigilance). In its report to the CPMP, that working party concluded:

... a causal relationship between the occurrence of valve heart disorders and the use of amfepramone could not [be] established. The benefit is considered unchanged compared to the previous CPMP opinion. [T]he benefit/risk balance of amfepramone-containing medicinal products remains unchanged.

29.

The Picon/Abadie Report, drawn up on 4 June 1998, states:

There is no clinical, epidemiological or experimental argument to evidence an association between amfepramone and the occurrence of heart valvular disease ... The benefit of amfepramone in the treatment of obesity is not modified ....

30.

By letters of 27 July 1998, the CPMP requested the holders of marketing authorisations of medicinal products containing amfepramone and phentermine to submit their observations on *inter alia* the benefit/risk balance of those medicinal products in the light of the Note for guidance on clinical investigation of drugs used in weight control, which was approved by the CPMP in December 1997 and came into effect in June 1998 (hereinafter the CPMP Note for Guidance).

31.

At its meeting of 17 September 1998, the CPMP decided to conduct the two procedures for amfepramone and phentermine separately from, but at the same time as, the procedure initiated on the same day concerning *inter alia* clobenzorex, fenproporex and norpseudoephedrine (see below, paragraph 62). In its report of 31 August 1999 on phentermine (see below, paragraph 55), the CPMP justified that decision on the grounds that medicinal products constituted only one of the factors in the treatment of obesity and that all the substances under consideration had the same pharmacological characteristics and the same indications.

32.

A new report supplementing the Picon/Abadie Report was drawn up in April 1999 (the Castot/Fosset Martinetti/Saint-Raymond Report). That report concluded:

[a]mfepramone does not fulfil the criteria of an effective therapy in obesity-treatment. Due to its potentials for tolerance and psychological dependence, amfepramone can only be used for less than three months, [which] contradicts current guidelines recommending long-term treatment. Considering the lack of therapeutic efficacy and the negative safety profile for long-term treatment (more than three months), the benefit/risk ratio of amfepramone is negative.

33.

On 12 April 1999, Professor Winkler sent to the members of the CPMP a discussion paper which drew attention to the negative evaluation of the benefit/risk balance of the substances under consideration, which had been made in the assessment reports on amfepramone (referred to above), on phentermine (see below, paragraph 47 et seq.), and also on clobenzorex,

fenproporex and norpseudoephedrine (see below, paragraph 61 et seq.), and summarised the oral observations made by the holders of the marketing authorisations concerned. As regards, in particular, the efficacy of those substances, it is apparent from that discussion paper that, in one oral question, the marketing authorisation holders had been requested to provide data showing that the substances evaluated made it possible to achieve either a long-term reduction in body weight, and thus had a therapeutic benefit (namely, a decrease in morbidity or mortality or an improvement in quality of life), or a short-term reduction in body weight carrying long-term advantages within an anti-obesity programme. In addition, in his discussion paper, Professor Winkler refuted the argument put forward by the marketing authorisation holders that there had been no new developments concerning the safety and efficacy of the substances under consideration. On the basis of the CPMP Note for Guidance and new national guidelines, he relied on the developments in the evaluation criteria in order to assert that there was now a □general consensus□ that the treatment of obesity requires a significant and long-term loss of weight (over more than one year). Medicinal products containing anorectic substances were therefore effective only if they were suitable for long-term use or if their short-term use resulted in a significant and lasting weight-loss. Furthermore, Professor Winkler stated that the introduction of new drugs to the market, namely □orlistat□ and □sibutramine□, apparently suitable for such long-term treatment, further demonstrated how the anorectic field had changed within a few years. Finally, he disputed the relevance of two new studies, the □Trenker Study□ on amfepramone, carried out by Professor Rottiers (1999), and the study on phentermine carried out by Professor Caterson and others, designed to show the long-term efficacy of those substances.

34.

On 22 April 1999, the CPMP issued its opinion (CPMP/969/99) on the scientific assessment of medicinal products containing amfepramone and recommended withdrawing the marketing authorisations of those products.

35.

The applicants appealed to the CPMP against that opinion, pursuant to the second sentence of Article 13(4) of Directive 75/319.

36.

In their report of 17 August 1999 on amfepramone, the rapporteur and co-rapporteur in the appeal procedure, Professors Garattini and de Andres-Trelles, recommended that medicinal products containing amfepramone be withdrawn from the market. In particular, they pointed out that very high risks were acceptable when compensated for by benefits. If the expected

benefit were near trivial, no level of potentially important risk could be accepted.

37.

On 27 August 1999, the applicants proposed carrying out further clinical trials of amfepramone.

38.

In its final opinion of 31 August 1999 (CPMP/2163/99), the CPMP rejected the applicants' appeals and, on the basis of an assessment of the benefit/risk balance, recommended withdrawing the marketing authorisations of medicinal products containing amfepramone.

39.

In its scientific conclusions annexed to that opinion, the CPMP stated:

"Therapeutic efficacy for treating obesity requires a significant and long-term lowering of body weight (at least one year). This is based on accumulated scientific knowledge acquired over the years and is laid down in current medical recommendations; this is reflected in the [CPMP Note for Guidance]. This is also expressed in current guidelines, e.g. the Scottish guideline (November 1996), a guideline from the Royal College of Physicians (1998) and in a guideline from the American Society for Clinical Nutrition (1998)."

40.

The CPMP found that, according to most of the available studies on amfepramone, when associated with a low-calorie diet that substance induced a weight-loss greater than a placebo. However, the mean effect was modest, never exceeding 5.1 kg whatever the duration of treatment. Moreover, no specific effect on recognised risk factors of obesity had been demonstrated. In addition, rapid weight-regain occurred once treatment was discontinued and there were no controlled studies demonstrating that a limited short-term effect provided any clinical benefit within a programme for the treatment of obesity. The Trenker Study on amfepramone failed to demonstrate the efficacy of treatment with amfepramone over a 12-month period given, first, the small number of patients included in the study (29 in the amfepramone group), the high drop-out rate (25%) and the unbalanced groups and, second, the modest loss of weight. On the subject of efficacy, the CPMP concluded that:

"in spite of the fact that nowadays obesity is considered a chronic disorder and that its management should be envisaged as a long-term strategy, amfepramone has only been shown to produce modest short-term weight-

reductions of dubious and unproven relevance for the outcome of the disorder. Its long-term effects remain unproven.

41.

As regards the safety of amfepramone, the CPMP essentially reiterated the undesirable effects already taken into consideration in the decision of 9 December 1996.

42.

With particular regard to the risk of PPH, it recalled that, in its opinions of 17 July 1996 (see above, paragraphs 23 and 24), it had relied on the IPPH Study to conclude that the risk of inducing PPH might be a class effect of amphetamine-like agents. However, data published subsequently had shown that study to be inconclusive on that matter. Noting that, in the data from spontaneous reporting, several cases of [PPH] with amfepramone have been reported, the CPMP found that:

in the absence of more formal epidemiological evidence, the possibility of an increased risk of [PPH] associated with amfepramone cannot currently be supported [or] refuted.

43.

Finally, after stating that 25 cases of cardiac valve disorders associated with amfepramone use, mostly in combination with fenfluramine or dexfenfluramine, had been spontaneously reported, it concluded:

[i]t would appear that amfepramone monotherapy does not increase the risk of cardiac valve disorders but, as ... is often the case in the absence of specifically-designed epidemiological studies, the possibility cannot be categorically excluded.

44.

As regards the benefit/risk balance, the CPMP considered that [o]n the basis of the available evidence on [amfepramone's] efficacy, it is no longer possible to consider that amfepramone has therapeutic efficacy in the treatment of obesity or (as a consequence) that its benefit/risk balance is positive.

45.

In a dissenting opinion appended to the CPMP final opinion of 31 August 1999, four members of that committee, Professor Hildebrandt, Dr Haase, Professor Odlind and Dr Sjöberg, declared themselves in favour of suspending, rather than withdrawing, the marketing authorisations of

medicinal products containing amfepramone, given the fact that obesity was □a significant health problem□. After pointing out, first, the absence of any significant new safety concerns since the CPMP opinion of 17 July 1996 and, second, the lack of data on the long-term efficacy of amfepramone, they referred to the particular need, in the light of □recent guidelines in the treatment of obesitas□, to carry out clinical trials in order to collect data long-term (over a period of more than one year) on the efficacy and safety of the substance in question.

46.

On 9 March 2000, the Commission adopted the contested decision, C(2000) 453.

Decision C(2000) 452 concerning the withdrawal of marketing authorisations of medicinal products which contain phentermine, contested in Cases T-132/00 and T-137/00

47.

On 19 November 1997, following a referral by the Belgian Ministry for Social Affairs, Public Health and the Environment (see above, paragraph 26), the CPMP initiated the procedure under Article 13 of Directive 75/319 in respect of phentermine used in monotherapy.

48.

The pharmacovigilance working party concluded in its report on phentermine, drawn up at its meeting of 12 to 14 May 1998, at which the co-rapporteur, Professor Hildebrandt, submitted his draft scientific report, that, as was the case for amfepramone (see above, paragraph 28), the evaluation of the efficacy of phentermine had not changed since the CPMP opinion of 17 July 1996.

49.

In his final scientific report on phentermine of 12 April 1999, the co-rapporteur concluded that that substance had a benefit/risk balance which was □not satisfactory□. As regards the benefits, he found that the efficacy of phentermine as an adjunctive treatment for obesity had been demonstrated in a small number of studies which included relatively few patients and did not conform to current standards. The weight-loss achieved was modest and there was no data on the long-term effects of phentermine and *a fortiori* on the maintenance of weight-loss. Consequently, most of the basic requirements laid down in the CPMP Note for Guidance were not met.

50.

On the same date, the aforementioned discussion paper drawn up by Professor Winkler (paragraph 33) was sent to the members of the CPMP.

51.

In its opinion of 22 April 1999 on phentermine (CPMP/968/99), the CPMP recommended withdrawing the marketing authorisations of medicinal products containing that substance. The applicants appealed to the CPMP against that opinion.

52.

By letter of 13 August 1999, the holders of marketing authorisations of medicinal products containing phentermine also proposed carrying out clinical trials to investigate its long-term efficacy.

53.

In their report of 17 August 1999 on phentermine, the rapporteur and co-rapporteur in the appeal procedure, Professors Garattini and de Andres-Trelles, proposed recommending the withdrawal of those marketing authorisations. They pointed out, *inter alia*, that the best available evidence for efficacy in longer-term use (but still over only 36 weeks) came from the 1968 report by Dr Munro and others. However, according to that study, the weight-loss was less than 10% of the original weight, applied only to a small percentage of patients and tended to diminish with the duration of the treatment. In addition, the weight-regain at the end of the treatment could result in the post-treatment weight exceeding the original weight. There were no studies of longer than 36 weeks. The available results did not constitute sufficient proof of the long-term efficacy of phentermine.

54.

On 31 August 1999, the CPMP issued its final opinion on phentermine, in which it recommended that the marketing authorisations of medicinal products containing that substance be withdrawn on the ground that the benefit/risk balance was unfavourable. It relied essentially on the same arguments as those set out in its final opinion on amfepramone (see above, paragraphs 39 to 44). Those two opinions gave rise to similar dissenting opinions (see above, paragraph 45).

55.

In its scientific conclusions annexed to its final opinion on phentermine, and in its report of 31 August 1999 on that substance, the CPMP first of all noted essentially that, according to the latest guidelines, therapeutic efficacy required a significant and long-term lowering of body weight (for at least one year). As regards phentermine in particular, it stated that, according to a

number of short-term studies, only a slight decrease in body weight can be achieved with phentermine. Moreover, no studies were available concerning the effects of phentermine on the risk factors of obesity. The new study relied on by certain marketing authorisation holders did not provide any additional relevant information. In addition, weight was rapidly regained after treatment was discontinued and there were no controlled studies demonstrating that a limited short-term effect had any clinical benefit within an obesity-treatment programme. The CPMP therefore concluded, in terms similar to those used in respect of amfepramone (see above, at the end of paragraph 40), that phentermine lacked therapeutic efficacy.

56.

In respect of safety, the CPMP also recalled the undesirable effects of the substances under consideration, which had already been taken into consideration by the Commission in its decision of 9 December 1996.

57.

However, as regards the risk of PPH, the CPMP acknowledged that phentermine had not been among the substances investigated in the IPPH Study on which it had based its opinion of 17 July 1996, and that, as a consequence, formal evidence from epidemiological studies is lacking. After observing that several cases of PPH associated with phentermine had been reported, it suggested that, in the absence of evidence that there is an association between phentermine and that medical condition, the possibility of an increased risk of [PPH] ... cannot be excluded.

58.

In respect of the risk of cardiac valve disorders, the CPMP pointed out that, in 1997, the United States Food and Drug Administration (hereinafter the FDA) had reported numerous cases of cardiac valve disorders in patients receiving fenfluramine in combination with phentermine and more than five cases of cardiac valve disorders associated with the use of phentermine in monotherapy. In two cases the treatment duration was less than three months. In the European Union, only 10 cases (in Belgium), associated with the combined use of phentermine and other anorectic agents, had been reported to the pharmacovigilance systems. The CPMP deduced that although there is not enough evidence to assert that phentermine increases the risk of cardiac valve disorders, such [a] hypothesis cannot be ruled out for the time being.

59.

The CPMP concluded, just as in respect of amfepramone (see above, paragraph 44), that the benefit/risk balance of phentermine was unfavourable on the ground of its lack of efficacy.

60.

On 9 March 2000, the Commission adopted the contested decision, C(2000) 452.

Decision C(2000) 608 concerning the withdrawal of marketing authorisations of medicinal products which contain, inter alia, clobenzorex, fenproporex and norpseudoephedrine, contested in Cases T-83/00, T-84/00 and T-85/00

61.

In its letter to the CPMP of 31 August 1998, prompted by the aforementioned referral to that committee in respect of phentermine and amfepramone (paragraph 26), the Austrian Federal Ministry for Labour, Health and Social Affairs pointed out that clobenzorex, fenbutrazate, fenproporex, mazindol, mefenorex, norpseudoephedrine, phenmetrazine, phendimetrazine and propylhexedrine belonged to the same group of amphetamine-related anorectics. It added that it was likely that all those substances shared the same effects and side effects and requested the CPMP to issue a reasoned opinion, under Article 15a of Directive 75/319, on all the medicinal products containing those substances. It pointed out that recent developments concerning the efficacy of anorectics (namely, the CPMP decisions in connection with new anti-obesity medicinal products, the CPMP Note for Guidance, and the cardiac valve disorders reported by the Belgian Government) justified a re-evaluation of the benefit/risk balance of those substances.

62.

On 17 September 1998, the CPMP initiated the procedure under Article 13 of Directive 75/319 in respect of the substances referred to in the Austrian request.

63.

The rapporteur and co-rapporteurs submitted their scientific assessment reports on those substances. On 12 April 1999, Professor Winkler's discussion paper, referred to above (paragraph 33), was sent to the members of the CPMP.

64.

On 22 April 1999, the CPMP issued an opinion on the substances under consideration, in which it recommended withdrawing the marketing authorisations for medicinal products containing those substances. The applicants appealed to the CPMP against that opinion.

65.

On 27 August 1999, the applicants proposed carrying out further clinical trials, in accordance with the latest CPMP guideline.

66.

In its final opinion of 31 August 1999 (CPMP/2164/99), the CPMP rejected the applicants' appeals and, on the basis of an analysis of the benefit/risk balance, recommended withdrawing the marketing authorisations for medicinal products containing, *inter alia*, clobenzorex, fenproporex and norpseudoephedrine. That CPMP opinion was the subject of a dissenting opinion similar to those annexed to the CPMP opinions on amfepramone and phentermine (see above, paragraph 45).

67.

In its scientific conclusions annexed to that opinion, the CPMP pointed out essentially, in the same terms as in its opinions on amfepramone and phentermine (see above, paragraphs 39 and 55), that according to the latest guidelines therapeutic efficacy in the treatment of obesity requires a significant and long-term lowering of body weight for at least one year.

68.

It noted that there were a very few double-blind placebo studies which showed that amphetamine-like substances could lower body weight at least for a short period and to a limited degree. The administration of higher doses resulted in more pronounced weight-loss, but was accompanied by significant side effects. Within weeks of treatment, pharmacological tolerance developed. Moreover, rapid weight-regain occurred once treatment was discontinued and there were no controlled studies demonstrating that a limited short-term effect provided any clinical benefit within an obesity-treatment programme. In addition, due to the risk of dependence associated with the substances examined, it had not been possible to carry out any studies to investigate whether, when used for more than three months, those substances induced a long-term reduction in weight. The CPMP concluded that, given current scientific knowledge and medical recommendations on the treatment of obesity, the substances examined lacked therapeutic efficacy when used for three months or less. Since it was not acceptable to prescribe those substances for longer than three weeks, their long-term use was of no relevance.

69.

In respect of safety, the CPMP pointed out the undesirable effects of the substances under consideration, which had already been reported in the decision of 9 December 1996.

70.

As regards, more specifically, the risk of PPH, the CPMP noted, as in respect of amfepramone (see above, paragraph 42), that according to data published subsequently the IPPH Study, on the basis of which it had concluded in its opinion of 17 July 1996 that there was a risk of PPH, was inconclusive in that regard. As to that risk, it stated:

taking into account data from spontaneous reports and in the absence of more formal epidemiological evidence, the possibility of an increased risk of PPH associated with these active substances cannot currently be ruled out.

71.

Finally, as regards the risk of cardiac valve disorders, the CPMP stated that no cases had been reported for the substances evaluated in the opinion. It found that, at that time, there was no evidence of a link between cardiac valve disorders and the use of those substances.

72.

The CPMP concluded, as in respect of amfepramone and phentermine, that the substances evaluated had an unfavourable benefit/risk balance on the ground of their lack of efficacy (see above, paragraph 44).

73.

On 9 March 2000, the Commission adopted Decision C(2000) 608.

Procedure

74.

By applications lodged at the Court Registry on 30 March, 3 and 6 April and 17, 22 and 25 May 2000 respectively, the applicants brought the present actions.

75.

By separate documents, lodged at the Court Registry on the same day as the principal applications, they submitted eight applications for suspension of the operation of the three contested decisions.

76.

By order of 28 June 2000 in Case T-74/00 R *Artegodan* v *Commission* [2000] ECR II-2583, the President of the Court of First Instance ordered suspension of the operation of Decision C(2000) 453 in respect of the applicant Artegodan. No appeal was lodged against that order.

77.

By order of 19 October 2000 in Case T-141/00 R *Trenker* v *Commission* [2000] ECR II-3313 and six other orders of 31 October 2000 in Cases T-76/00 R *Bruno Farmaceutici and Others* v *Commission* [2000] ECR II-3557, T-83/00 R II *Schuck* v *Commission* [2000] ECR II-3585, T-84/00 R *Roussel and Roussel Diamant* v *Commission* [2000] ECR II-3591, T-85/00 R *Roussel and Roussel Iberica* v *Commission* [2000] ECR II-3613, T-132/00 R *Gerot Pharmazeutika* v *Commission* [2000] ECR II-3635 and T-137/00 R *Cambridge Healthcare Supplies*v *Commission* [2000] ECR II-3653, the President of the Court of First Instance also ordered suspension of the operation of the three contested decisions in respect of the applicants in those cases. The Commission appealed against those seven orders. By orders of 11 April 2001 in Cases C-459/00 P(R) *Commission* v *Trenker* [2001] ECR I-2823, C-471/00 P(R) *Commission* v *Cambridge Healthcare Supplies* [2001] ECR I-2865, C-474/00 P(R) *Commission* v *Bruno Farmaceutici and Others* [2001] ECR I-2909, C-476/00 P(R) *Commission* v *Schuck* [2001] ECR I-2995, C-477/00 P(R) *Commission* v *Roussel and Roussel Diamant* [2001] ECR I-3037, C-478/00 P(R) *Commission* v *Roussel and Roussel Iberica* [2001] ECR I-3079 and C-479/00 P(R) *Commission* v *Gerot Pharmazeutika* [2001] ECR I-3121, the President of the Court of Justice set aside the orders of the Court of First Instance and dismissed the applications for interim relief.

78.

In Case T-74/00 R *Artegodan* v *Commission*, cited above, the Commission sought, by application lodged at the Court Registry on 20 April 2001, the cancellation, under Article 108 of the Rules of Procedure of the Court of First Instance, of the aforementioned order of the President of the Court of First Instance of 28 June 2000. By order of 5 September 2001 ([2001] ECR II-2367), the President of the Court of First Instance dismissed that application. On 13 November 2001, the Commission brought an appeal against that order. By order of 14 February 2002, the Court of Justice set aside the order of 5 September 2001 and cancelled the aforementioned order of 28 June 2000, thereby ending the suspension of the operation of the contested decision (C(2000) 453) as regards Artegodan (Case C-440/01 P(R) *Commission* v *Artegodan* [2001] ECR I-1489).

79.

In its application, the applicant in Case T-141/00 had sought to have that case joined with Case T-76/00. By order of 23 July 2001, after hearing all the parties, the President of the Second Chamber ordered that Cases T-74/00, T-76/00, T-83/00, T-84/00, T-85/00, T-132/00, T-137/00 and T-141/00 be joined for the purposes of the oral procedure and of the final judgment.

80.

By decision of 14 March 2002, the Court of First Instance referred the cases to the Second Chamber, Extended Composition, in accordance with Article 51(1) of its Rules of Procedure.

81.

By order of 25 April 2002, the President of the Second Chamber, Extended Composition, after hearing all the parties, ordered that the aforementioned cases and Case T-147/00 be joined for the purposes of the oral procedure.

82.

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 reply to a number of written questions from the Court and to produce certain documents. They complied with those requests.

83.

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.

Forms of order sought

84.

In Case T-74/00, the applicant claims that the Court should:

- annul Commission Decision C(2000) 453 of 9 March 2000;

- in the alternative, annul that decision in so far as Article 1 thereof, in conjunction with Annex I thereto, requires Germany to withdraw the marketing authorisation of the medicinal product "Tenuate Retard", containing amfepramone, marketed by the applicant;

- order the Commission to pay the costs.

85.

In Case T-76/00, the applicants claim that the Court should:

- annul Commission Decision C(2000) 453 of 9 March 2000;

- in the alternative, annul that decision in so far as Article 1 thereof, in combination with Annex I thereto, requires Belgium, Denmark, Germany, the United Kingdom, France, Italy, Luxembourg, Austria and Spain to withdraw the marketing authorisations of the medicinal products containing amfepramone which are marketed by the applicants;

- order the defendant to pay the costs.

86.

In Case T-141/00, the applicant claims that the Court should:

- annul Commission Decision C(2000) 453 of 9 March 2000;

- order the defendant to pay the costs.

87.

In Case T-83/00, the applicant claims that the Court should:

- annul Commission Decision C(2000) 608 of 9 March 2000;

- in the alternative, annul that decision in so far as Article 1 thereof, in conjunction with Annex I thereto, requires Germany to withdraw the marketing authorisations of the medicinal product containing norpseudoephedrine which is marketed by the applicant;

- order the defendant to pay the costs.

88.

In Case T-84/00, the applicants claim that the Court should:

- annul Commission Decision C(2000) 608 of 9 March 2000;

- in the alternative, annul that decision in so far as Article 1 thereof, in conjunction with Annex I thereto, requires France and Portugal to withdraw the marketing authorisations of the medicinal products containing clobenzorex, which are marketed by the applicants;

- order the defendant to pay the costs.

89.

In Case T-85/00, the applicants claim that the Court should:

- annul Commission Decision C(2000) 608 of 9 March 2000;

- in the alternative, annul that decision in so far as Article 1 thereof, in conjunction with Annex I thereto, requires Spain and Portugal to withdraw the marketing authorisations of the medicinal products containing fenproporex which are marketed by the applicants;

- order the defendant to pay the costs.

90.

In Case T-132/00, the applicant claims that the Court should:

- annul Commission Decision C(2000) 452 of 9 March 2000;

- in the alternative, annul that decision in so far as Article 1 thereof, in conjunction with Annex I thereto, requires Austria to withdraw the marketing authorisations of the medicinal product Adipex Retard-Kapseln containing phentermine which is marketed by the applicant;

- order the defendant to pay the costs.

91.

In Case T-137/00, the applicant claims that the Court should:

- annul Commission Decision C(2000) 452 of 9 March 2000;

- order the defendant to pay the costs.

92.

In the eight joined cases, the defendant contends that the Court should:

- dismiss the applications;

- order the applicants to pay the costs.

Law

93.

In support of their applications for annulment, the applicants rely on a series of pleas in law which it is appropriate to classify and group together as follows: first, the Commission's lack of competence and, second, infringement of Articles 11 and 21 of Directive 65/65, of Article 15a of Directive 75/319 and of the principles of non-retroactivity, legal certainty and proportionality, as well as breach of essential procedural requirements, manifest error of assessment and misuse of powers. The applicants also rely on, third, alleged amendment of the subject-matter of the arbitration procedures initiated at Belgium's request; fourth, failure to observe the time-limits laid down in

Articles 13 and 14 of Directive 75/319; fifth, infringement of the right of the undertakings concerned to be heard; sixth, infringement of certain provisions of Directive 75/318 and, seventh, breach of the obligation to state reasons.

1. *The plea alleging the Commission's lack of competence to take the contested decisions*

Pleas in law and arguments of the parties

94.

All the applicants submit that the Commission was not competent to adopt the contested decisions. They claim that the marketing authorisations of the medicinal products in question are purely national and that, consequently, Article 15a of Directive 75/319 does not provide the Commission with a valid legal basis for taking those decisions. That article allows a Member State to initiate the Community decision-making procedure provided for in Articles 13 and 14 of Directive 75/319 only in respect of authorisations granted in accordance with the provisions of Chapter III of that directive.

95.

In that regard, the applicants point out that in the Community there are three co-existing marketing authorisation procedures for medicinal products: the procedure for authorisation by the competent national authorities, provided for in Article 3(1) of Directive 65/65, the decentralised Community procedure established by Chapter III of Directive 75/319 and, finally, the centralised Community procedure established by Regulation No 2309/93.

96.

In the present case, contrary to the Commission's contention, the fact that the national marketing authorisations in question were supplemented by the decision of 9 December 1996, which was the outcome of a procedure based on Article 12 of Directive 75/319, does not permit the inference that they were granted in accordance with the provisions of Chapter III of that directive and thus fall within the scope of Article 15a.

97.

In the decision of 9 December 1996, the Commission merely amended certain particulars in the summary of product characteristics. Even assuming that that decision partially harmonised the marketing authorisations of the medicinal products in question, such a harmonisation cannot be treated as equivalent to the grant of a marketing authorisation under the provisions of Chapter III of Directive 75/319.

98.

The applicants in Cases T-76/00, T-83/00, T-84/00, T-85/00, T-132/00 and T-141/00 claim that Article 15a of Directive 75/319 clearly states that the Community arbitration procedure provided for therein applies only to marketing authorisations granted in accordance with the mutual recognition procedure referred to in Article 9 of that directive. In the scheme of Chapter III of Directive 75/319, the aim of Article 15a is to ensure that the harmonisation attained when a marketing authorisation is issued by way of mutual recognition is maintained if a subsequent amendment or the withdrawal of that marketing authorisation appears necessary to a Member State on grounds of protection of public health. In that system, marketing authorisations which have not been the subject of mutual recognition are purely national and therefore cannot, under any circumstances, be the subject-matter of a Community arbitration procedure under Article 15a.

99.

The applicant in Case T-74/00 takes the view that Article 15a of Directive 75/319 applies to marketing authorisations granted by way of mutual recognition, under Article 9 of that directive, or in accordance with the procedures provided for in Articles 10 and 11 of the directive. By contrast, the procedure for consultation of the CPMP established by Article 12 of that directive cannot result in an authorisation granted in accordance with the provisions of [Chapter III].

100.

The applicant in Case T-137/00 considers that Articles 15 and 15a of Directive 75/319 establish mandatory arbitration procedures in cases where a marketing authorisation has been granted by way of mutual recognition or following a referral to the CPMP under Articles 10, 11 or 12 of that directive. It claims that, as a result of the intervention of the CPMP, the grant of authorisation has already been subject to a degree of harmonisation. It therefore makes sense that the authorisation may only be varied, suspended or withdrawn by a decision which is uniform throughout the Community. By contrast, the Member States remain competent to vary, suspend or withdraw a marketing authorisation granted on the basis of a purely national procedure, even where that authorisation has already been subject to variation following a CPMP opinion under Article 12 of Directive 75/319. In that context, the Member States have the option of making a referral to the CPMP under Articles 11 and 12 of that directive in order to obtain a consultative opinion.

101.

In support of their arguments, the applicants in Cases T-74/00 and T-137/00 maintain that Article 12 of Directive 75/319 does not allow for even the partial harmonisation of national marketing authorisations. That article does

not empower the Commission to adopt a binding decision. Just like Articles 10 and 11 of that directive, it does no more than expressly provide for consultation of the CPMP in accordance with the procedure laid down in Article 13 of that directive. The decision of 9 December 1996 is therefore unlawful and cannot provide the basis for the Commission's competence under Article 15a of that directive.

102.

In reply to a question put by the Court at the hearing, all the applicants pointed out that Articles 15 and 15a of Directive 75/319 expressly provide for the application of the procedures laid down in Articles 13 and 14 of that directive. In that context, the lack of any reference in Articles 10, 11 and 12 of Directive 75/319 to the decision-making procedure governed by Article 14 is not a drafting omission, as is clear from the strictly identical wording of the corresponding articles in the Code.

103.

Furthermore, the applicant in Case T-74/00 adds that, given, in particular, the object and the purpose of Article 15a of Directive 75/319, the procedure which it prescribes is not applicable by analogy to national marketing authorisations which have been varied in part under Article 12 of that directive. Under the procedure for mutual recognition provided for in Article 9 of that directive, all the information and particulars referred to in Articles 4, 4a and 4b of Directive 65/65 - which have been sent to the competent authority of a Member State for the purpose of obtaining a national marketing authorisation - are submitted, under Article 9(1) of Directive 75/319, to the competent authorities of the Member States which have received applications for recognition of the initial national authorisation. It is the concurrent examination of that abundant documentation by the Member States which, according to the applicant, justifies the arbitration procedure provided for in Article 15a of Directive 75/319. There is no such justification in the case of a purely national authorisation which has been varied in accordance with Article 12 of the directive.

104.

The Commission rejects that line of argument. It follows from the wording of Article 15a of Directive 75/319, which expressly refers to authorisations granted in accordance with the provisions of Chapter III - which contains Articles 8 to 15b -, that that article does not refer solely to marketing authorisations granted under the mutual recognition procedure provided for in Article 9 of that directive but also covers marketing authorisations harmonised under Article 12 of that directive.

105.

In addition, a teleological interpretation of Article 15a of Directive 75/319 confirms that a marketing authorisation harmonised under Article 12 of that directive falls within the scope of Article 15a. Just as in the case of Articles 15 and 15b of that directive, the aim of Article 15a is to prevent unilateral national measures from jeopardising a uniform assessment of specific medicinal products or groups of medicinal products, in order to protect public health and safeguard the single market.

106.

In particular, the purpose of Article 15a precludes a narrow interpretation excluding partial harmonisation from the scope of that article. In that regard, the Commission recalls that it pointed out in point 7 of its Communication 98/C 229/03 of 22 July 1998 on the Community marketing authorisation procedures for medicinal products (OJ 1998 C 229, p. 4) that [t]he principle that achieved harmonisation has to be maintained is ... not limited to products which have undergone mutual recognition ... it also covers all other cases in which a [summary of product characteristics] was fully or partly harmonised through any Community procedure.

107.

In the present case, the decision of 9 December 1996, based on Article 12 of Directive 75/319, partly harmonised at European level the national marketing authorisations of medicinal products containing substances referred to in the contested decisions, by requiring Member States significantly to amend the summaries of product characteristics relating to those medicinal products. The summary of product characteristics, referred to in Article 4a of Directive 65/65, constitutes the core of the marketing authorisation of a medicinal product. More specifically, the clinical particulars in that summary, referred to in Article 4a(5) of that directive, are the most direct means of safeguarding public health, which is the primary purpose of Directive 65/65 (first recital in the preamble). The authorisations of the medicinal products under consideration in the present case were therefore significantly and radically amended by the decision of 9 December 1996.

108.

On that point, the Commission disputes the applicants' argument that the decision of 9 December 1996 did not harmonise the marketing authorisations for the medicinal products in question, since Article 12 of Directive 75/319 does not provide for the application of the decision-making procedure governed by Article 14 of that directive. It asserts that Articles 13 and 14 of that directive establish a single procedure, inasmuch as Article 14(1) provides

that the Commission is to prepare a draft decision after receipt of the CPMP opinion forwarded to it in accordance with Article 13(5).

109.

At the hearing, the Commission added, in reply to a question from the Court, that all the provisions of Chapter III of Directive 75/319 must be interpreted in the light of the purpose specified in Article 8 of that directive, which is to facilitate the adoption by the Member States of common decisions on the authorisation of medicinal products. The pursuit of that objective finds its concrete expression in the automatic application of the decision-making procedure provided for in Article 14 of that directive following consultation of the CPMP in accordance with Article 13 thereof. That objective is supported by the fourth recital in the preamble to Directive 93/39 which essentially states that, in the event of disagreement between Member States in the mutual recognition procedure, a referral is to be made to the CPMP leading to a single decision, and by Article 7a of Directive 65/65, which requires a Member State which considers that the marketing authorisation of a medicinal product granted by another Member State may present a risk to public health to apply □the procedures set out in Articles 10 to 14 of Directive 75/319/EEC□. The inseparable nature of the procedures provided for in Articles 13 and 14 - as confirmed by Article 7a of Directive 65/65 and the fourth recital in the preamble to Directive 93/39, in connection with Article 10 of Directive 75/319 - also holds true in connection with Article 12 of that directive, because that article refers to □specific cases where the interests of the Community are involved□. In the present case, the decision of 9 December 1996 was thus validly adopted.

110.

In any event, that decision was not contested by the applicants in sufficient time, and its validity can thus no longer be challenged. The harmonisation of the national marketing authorisations carried out in 1996 must therefore be maintained, irrespective of the question of interpretation of Article 12 of Directive 75/319, which is of no relevance to the present case. In those circumstances the withdrawal of those authorisations fell in any event, according to the Commission's replies to questions put by the Court at the hearing, within the competence conferred on it by Article 15a of Directive 75/319.

111.

Finally, the Commission claims that the applicants' contention would result in a situation where, notwithstanding a Community harmonisation decision under Article 12 of Directive 75/319, medicinal products could continue to be authorised in some Member States and be the subject of a decision

withdrawing their marketing authorisation in others, a situation which would be incompatible with a single market. In addition, that contention does not take account of the fact that the Member States in any event participate in the procedure established by Article 15a(1) of Directive 75/319 inasmuch as they are represented on the Standing Committee on Medicinal Products for Human Use.

Findings of the Court

112.

It is appropriate at the outset to clarify the legal rules applicable to the marketing authorisations of the medicinal products referred to by the contested decisions, in the light of the relevant principles of transitional law, and then to determine the legal implications of the dispute as to the effects of the decision of 9 December 1996, before examining the relevant provisions of Chapter III of Directive 75/319 in order to determine whether the withdrawal of the authorisations in question fell within the competence of the Commission.

The legal rules applicable to the marketing authorisations of the medicinal products referred to by the contested decisions, in the light of the principles of transitional law

113.

It is common ground between the parties that the marketing authorisations of the medicinal products referred to by the contested decisions were granted, and in some cases renewed, in accordance with the national procedures applicable in the various Member States concerned, and not in accordance with the mutual recognition procedure coupled with arbitration procedures, provided for in Chapter III of Directive 75/319.

114.

Leaving aside the decision of 9 December 1996, those authorisations were thus purely national. Disregarding that decision, the suspension, variation or withdrawal of those authorisations therefore came, at the time when the contested decisions were adopted, within the exclusive competence of the Member States concerned, a competence which, following the introduction of the mutual recognition procedure by Directive 93/39, is essentially residual.

115.

Since 1 January 1998, there have been only two autonomous, distinct procedures for authorisation and monitoring of medicinal products co-existing in the Community: the centralised Community procedure established by Regulation No 2309/93, which has been applicable since 1 January 1995,

and the decentralised Community authorisation procedure, in the words of the eighth recital in the preamble to Regulation No 2309/93. The latter procedure, also applicable since 1 January 1995, was set up, in Chapter III of Directive 75/319, in the form of a procedure for the mutual recognition of the initial national marketing authorisation of the medicinal product in question - issued by the reference Member State in accordance with the common criteria of quality, safety and efficacy set out in Directive 65/65 - together with Community arbitration procedures, applicable where the mutual recognition procedure is frustrated and in respect of the management of marketing authorisations which come within the scope of those arrangements.

116.

In those circumstances, by defining the scope of the mutual recognition procedure, Article 9 of Directive 75/319 and Articles 7 and 7a of Directive 65/65 serve to define *a contrario* the essentially residual field of exclusive competence of the Member States. Since 1 January 1995 that exclusive competence has been restricted to, first, the grant and management of marketing authorisations for medicinal products marketed solely in a single Member State and, second, the management of purely national marketing authorisations granted before that date or during the transitional period from 1 January 1995 to 31 December 1997. The relevant provisions of Chapter III of Directive 75/319 expressly provide for a Community procedure to be applied in the management of only those authorisations granted under the provisions of that chapter. Moreover, it is clear from Article 4 of Directive 93/39, in conjunction with Article 7a of Directive 65/65, that, during the transitional period, the Member States were competent to grant marketing authorisations in respect of medicinal products which had already been marketed in one or more other Member States in cases where the applicant opted for the national marketing authorisation procedure rather than the mutual recognition procedure.

117.

The present dispute comes within the ambit of the system described above, which has been applicable since 1 January 1995. According to the principles of transitional law, that new system could be applied immediately in respect of the future consequences and the management, from that date on, of the marketing authorisations previously granted (see, to that effect, Case 1/73 *Westzucker* [1973] ECR 723, paragraph 5). In the present case, the national authorisations in question were thus immediately subject to the relevant provisions of Directive 75/319, as amended by Directive 93/39.

118.

In this case, the effect of the decision of 9 December 1996 on the classification of those authorisations and, accordingly, the competence of the Commission to adopt the contested decisions must therefore be assessed in the light of those rules.

The legal implications of the dispute as to the effects of the decision of 9 December 1996

119.

It is for the Court to determine whether, following their amendment pursuant to the decision of 9 December 1996, the marketing authorisations of the medicinal products referred to by the contested decisions fell within the scope of Article 15a(1) of Directive 75/319.

120.

In that regard, it should be noted at the outset that the Commission correctly submits that that amendment concerned an essential aspect of the aforementioned authorisations (see above, paragraph 107). In reality, those authorisations were partially harmonised, although the question remains as to whether that harmonisation was the consequence of a binding decision, validly adopted by the Commission.

121.

Article 15a(1) of Directive 75/319 refers to marketing authorisations granted in accordance with the provisions of [Chapter III] of that directive. It essentially provides that the variation, suspension or withdrawal of such authorisations, on the initiative of a Member State with a view to the protection of public health, fall within the exclusive competence of the Commission, when adopting a decision following a CPMP opinion in accordance with the procedures laid down in Articles 13 and 14 of Directive 75/319. Conversely, the variation, suspension and withdrawal of marketing authorisations which do not fall within the ambit of Article 15a remain, in principle, subject to the exclusive competence of the Member States.

122.

In the present case, the applicants submit essentially that national authorisations, harmonised under a procedure based on Article 12 of Directive 75/319, continue to come within the exclusive competence of the Member States.

123.

The defendant, relying, in particular, on its communication of 22 July 1998, claims that the management of those authorisations comes within the scope of a community arbitration procedure.

124.

That communication cannot provide an authoritative interpretation of the relevant provisions. It can only serve to make known the Commission's interpretation of the rules governing the Community procedures relating to the marketing authorisations of medicinal products. While, in such a communication, the Commission is entitled to clarify, and even supplement, specific provisions of the applicable legislation with a view to ensuring their practical efficacy, that communication cannot have the effect of amending the mandatory rules set out in that legislation (see, to that effect, Case C-322/93 P *Peugeot* v *Commission* [1994] ECR I-2727, paragraphs 12 and 15, and Case T-9/92 *Peugeot* v *Commission* [1993] ECR II-493, paragraphs 44 and 46). In particular, it cannot require the application of a Community arbitration procedure which is not provided for in the applicable legislation.

125.

In this case, the wording of Articles 12 and 15a of Directive 75/319 provides no clear guidance. It is therefore necessary to consider whether, in the scheme of Chapter III of that directive, and in the light of the aims of that directive, Article 15a(1), in conjunction with Article 12, can be construed as also applying to national marketing authorisations which have been harmonised under Article 12.

126.

To that end, having regard to the facts of the case and the arguments of the parties, the Court must determine, first, whether - as the Commission submits - Article 12 establishes an arbitration procedure which transfers competence from the Member States concerned to the Community. In the scheme of Chapter III of Directive 75/319, the variation, withdrawal and suspension of marketing authorisations harmonised within the framework of an arbitration procedure are necessarily governed by Article 15a of that directive. In that respect, since the mutual recognition procedure established by Chapter III of Directive 75/319 provides for the adoption of common decisions, there is no need, when considering whether such authorisations meet the criteria for application of Article 15a(1) of that directive, to distinguish between harmonisation which took place when the original authorisations were granted and harmonisation which occurred later, when those authorisations were substantively amended.

127.

Conversely, if Article 12 must be interpreted as establishing a merely consultative procedure, the decision of 9 December 1996 has no legal basis. On that view, although the decision is now definitive since it was not challenged in sufficient time, it cannot have the effect of altering the division of powers between the Member States and the Community laid down in the relevant legislation on the withdrawal of marketing authorisations. In that case, it is necessary to consider, second, whether national marketing authorisations of medicinal products voluntarily harmonised by the Member States following a CPMP opinion under Article 12 of Directive 75/319 can be placed on the same footing as marketing authorisations granted in accordance with the provisions of [Chapter III] of that directive.

The authority competent to adopt a decision following a CPMP opinion under Article 12 of Directive 75/319

128.

It is necessary to determine whether, despite the fact that Article 12 of Directive 75/319 does no more than expressly provide for the application of the consultative procedure set out in Article 13, a referral to the CPMP under Article 12 of that directive (Article 31 of the Code) has the effect of conferring on the Commission the competence to adopt a decision under the decision-making procedure provided for in Article 14 of that directive. To that end, after first examining the main provisions relating to the mutual recognition procedure, Article 12 of Directive 75/319 must be interpreted in the context of Chapter III of that directive. Given the lack of clarity and, consequently, transparency of certain provisions of Chapter III of Directive 75/319, a detailed examination of the provisions, albeit not applicable in the present case, relating to the mutual recognition procedure is essential for the purposes of a systemic interpretation of Article 12 of that directive.

129.

First, it should be recalled that in the mutual recognition procedure established by Article 9(4) of Directive 75/319 (Article 28(4) of the Code), the Member States concerned are to recognise the initial marketing authorisation granted by the reference State within 90 days of receipt of the application and the assessment report drawn up by that State, save in the exceptional case provided for in Article 10(1) of that directive (Article 29(1) of the Code), in which a Member State declines to recognise the initial authorisation.

130.

In such a case, Article 10(2) of that directive (Article 29(2) of the Code) provides for the application of a two-stage procedure. First, all the Member States concerned shall use their best endeavours to reach agreement on the

action to be taken in respect of the application. If they do not reach agreement by the time-limit referred to in the previous paragraph then, as a second stage, they are to refer the matter to the CPMP for the application of the procedure laid down in Article 13. That procedure is purely consultative.

131.

It follows that while Articles 15 and 15a of Directive 75/319 expressly provide for the application of the procedures laid down in Articles 13 and 14 of that directive, Article 10(2) does not expressly establish a Community arbitration procedure in cases where concertation between the Member States has failed. It is thus necessary to consider the legal implications of the lack of any express reference to the decision-making procedure laid down in Article 14, in the context of the mutual recognition procedure.

132.

It must be stated in this respect that the purpose of the mutual recognition procedure militates against a literal interpretation of Article 10(2) of Directive 75/319 which would preclude application of the procedure provided for in Article 14. Recital 12 in the preamble to the Code, which essentially reproduces the fourth recital in the preamble to Directive 93/39 establishing the mutual recognition procedure, states that a marketing authorisation for a medicinal product granted by a competent authority in one Member State ought to be recognised by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorisation of the medicinal product concerned may present a risk to public health. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to a Community standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States. Furthermore, the eighth recital in the preamble to Regulation No 2309/93 confirms that Directive 93/39 has provided that if such a disagreement between Member States occurs, the matter should be resolved by a binding Community decision following a scientific evaluation of the issues involved within [the CPMP].

133.

Article 10(2) of Directive 75/319 must therefore be interpreted, in conjunction with recital 12 in the preamble to the Code, as meaning that if the Member States have not overcome their differences within the prescribed period, they are obliged to initiate an arbitration procedure by referring the matter to the CPMP for application of the procedures set out in Articles 13 and

14 of that directive. In that context, the close cooperation between the Commission and the Member States referred to in recital 12 in the preamble to the Code finds its concrete expression in the implementation of the regulatory procedure, in which the Commission is assisted by the Standing Committee on Medicinal Products for Human Use, consisting of representatives of the Member States with a representative of the Commission as chairman, in accordance with Article 2b of Directive 75/318.

134.

That interpretation is compatible with the wording of Articles 13 and 14 of Directive 75/319. As pointed out by the Commission, Article 13(5) requires the CPMP opinion to be forwarded at the end of the consultative procedure not only to the Member States and the relevant marketing authorisation holders, but also to the Commission. In addition, while Article 13(1) provides that the CPMP is to consider the matter and issue an opinion [w]hen reference is made to the procedure described in this article, Article 14 merely states that, within 30 days of the receipt of the opinion, the Commission is to prepare a draft decision and refers to the regulatory procedure for adoption of the final decision. It is thus clear that the procedures set out in Articles 13 and 14 of Directive 75/319 are in principle intended to be automatically linked and to culminate in a community decision. Against that background, a teleological and systemic interpretation of Article 10(2) of that directive makes it possible to fill a gap in the drafting of Article 10 caused by the lack of any express reference to the procedure laid down in Article 14.

135.

Furthermore, it is only that interpretation which confers any practical effect on the provisions relating to the mutual recognition procedure. In particular, when the two-stage procedure established by Article 10(2) of Directive 75/319 is implemented, the second stage, which is triggered in precisely the case where concertation between the Member States has failed in the first stage, would risk being rendered redundant if it were purely consultative. Moreover, if the second stage of the procedure were considered to be consultative, even though earlier legislation had already provided for obligatory consultation of the CPMP in certain circumstances, the introduction by Directive 93/39 of a first stage of concertation prior to referral to the CPMP would merely delay the consultation of that committee. In view of the progressive harmonisation of the rules on medicinal products, the introduction of a two-stage procedure can therefore be logically justified only if the second stage consists in arbitration which is binding on the Member States.

136.

Against that background, the Court must determine, second, whether, in the scheme of Chapter III of Directive 75/319 and having regard to the objectives pursued, Article 12 of that directive can, like Article 10(2), be interpreted as impliedly providing for application of the procedure governed by Article 14.

137.

Article 12, cited above (paragraph 10), was substantially amended by Directive 93/39. The previous version of that article (as amended by Directive 83/570) stated:

'The competent authorities of Member States may, in specific cases where the interests of the Community are involved, refer the matter to the [CPMP] before reaching a decision on a request for a marketing authorisation or on the suspension or revocation of an authorisation.'

138.

The amendments made to Article 12 by Directive 93/39 do not however permit the inference that that article, in its amended form, establishes an arbitration procedure. The amendments did no more than, first, extend to the Commission and applicants or holders of marketing authorisations the right, previously held only by the Member States, to refer a matter to the CPMP. Accordingly, it is no longer expressly apparent from the wording of Article 12 that the power to adopt the final decision lies with the authorities of the Member States concerned, an omission which can be put down to drafting considerations, given the extension of the right to refer matters to the CPMP. Second, emphasis was placed on the fact that a matter can be referred to the CPMP, in particular to take account of the information collected in connection with pharmacovigiliance. Moreover, it became possible to refer a matter not only before reaching any decision on a request for a marketing authorisation or on the suspension or withdrawal of an authorisation, but also before any variation to the terms of an authorisation.

139.

In those circumstances, the Commission is competent to adopt decisions on national marketing authorisations following a referral to the CPMP under Article 12 of Directive 75/319 only if that competence is clearly apparent from the purpose of that provision or is expressly provided for in the system established by Chapter III of that directive.

140.

In contrast to Article 10(2) of Directive 75/319, which relates to the mutual recognition procedure and must accordingly be interpreted in accordance with the purpose of that procedure, as specifically defined in recital 12 in the

preamble to the Code, Article 12 of Directive 75/319, like Article 11 of that directive, is not one of the provisions providing the framework for the mutual recognition procedure. That procedure is expressly governed by Articles 9 and 10 on the grant of marketing authorisations, and Articles 15 and 15a on their management.

141.

Furthermore, contrary to the Commission's contentions, Article 8 of Directive 75/319 does not support an interpretation of Article 12 of that directive to the effect that it establishes a community arbitration procedure or that the opinion issued by the CPMP and forwarded, *inter alia*, to the Member States is binding on them. Article 8 merely states that the CPMP has been set up in order to facilitate the adoption of common decisions by Member States on the authorisation of medicinal products. The French version of that article - which, in referring to the adoption by the Member States of □une attitude commune□ (□a common position□), reproduces the wording of that provision prior to its amendment by Directive 93/39 and thereby differs on that point from the other language versions - contains a drafting error in that respect.

142.

For all those reasons, in the scheme of Chapter III of Directive 75/319, Article 12 of that directive, which does not include any express definition of its scope, 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 (see above, paragraphs 115 and 116). Against that background, it makes sense that that article provides for consultation of the CPMP only under Article 13. The Member States, which have the mere option to consult the CPMP, must not 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.

143.

In that regard, contrary to the defendant's contentions, the concept of □interests of the Community□, which determines the scope of Article 12 of Directive 75/319 and which provided grounds for consultation of the CPMP pursuant to that article even before the introduction of Community arbitration procedures by Directive 93/39, cannot legitimate such a transfer of competence in the absence of express provisions to that effect.

144.

Moreover, the wording of Articles 13(5) and 14(1) of Directive 75/319, which confirms that the consultative procedure and the Community decision-making

procedure are in principle intended to be linked (see above, paragraph 134), does not, of itself, permit Article 12 to be interpreted as establishing a Community arbitration procedure. The aforementioned provisions of Articles 13 and 14, relied on by the defendant, are purely procedural. In the absence of any provision expressly providing for a transfer of competence to the Community, those provisions therefore do not provide any guidance on the interpretation of Article 12 of Directive 75/319. In the scheme of Chapter III of Directive 75/319, the automatic link between the consultative procedure and the decision-making procedure, given concrete expression in Articles 13(5) and 14(1) of that directive, specifically relates to the mutual recognition procedure, which is precisely the subject of that chapter, a chapter which is indeed reproduced in Chapter 4 of Title III of the Code, under the heading ‘Mutual recognition of authorisations’.

145.

In addition, the fact that Article 15a(2) of Directive 75/319 entitles a Member State, in exceptional circumstances, ‘without prejudice to the provisions of Article 12’, to suspend the marketing authorisation of a medicinal product pending the adoption of a definitive decision does not provide any guidance on the interpretation of Article 12.

146.

Finally, in the scheme of Chapter III of Directive 75/319, the difference in kind between the procedures established by Articles 11 and 12 on the one hand, and the arbitration procedure established by Article 10(2), on the other, is also demonstrated by the essential differences in the documents to be forwarded to the CPMP. While, in the arbitration procedure, the CPMP is sent all the documents and information referred to in particular in Article 4 of Directive 65/65, Articles 11 and 12 provide only that ‘[t]he Member State[s] and the person responsible for placing the medicinal product on the market shall forward to the [CPMP] all available information relating to the matter in question’. Those factors confirm the purely consultative nature of the procedures established by Articles 11 and 12.

147.

It follows that, in the scheme of Chapter III of Directive 75/319 and in the light of its objectives, Article 12 cannot be interpreted as implicitly empowering the Commission to adopt a binding decision under the procedure set out in Article 14.

148.

However, in the present case, since the decision of 9 December 1996 has been complied with by the Member States concerned, it is necessary to

consider whether, in the scheme of Chapter III of that directive, authorisations harmonised by the Member States following consultation of the CPMP under Article 12 of Directive 75/319 can nevertheless be placed on the same footing as marketing authorisations granted in accordance with the provisions of Chapter III (see paragraph 127 above).

The classification of national marketing authorisations harmonised by the Member States following a CPMP opinion under Article 12 of Directive 75/319

149.

The system of harmonisation set up by Chapter III of Directive 75/319 is, as has already been observed (see above, paragraphs 115 and 128 to 135), based on the principle of mutual recognition in association with binding arbitration procedures. Against that background, national marketing authorisations which have been harmonised in accordance with a CPMP opinion under Article 12 of that directive are not, in principle, included in the concept of a marketing authorisation granted in accordance with the provisions of [Chapter III] within the meaning of Article 15a(1) of that directive.

150.

As the Court has already held (see above, paragraphs 136 to 147), Article 12 of Directive 75/319 sets up, 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 those circumstances, 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 15a(1) of Directive 75/319 to the effect that the harmonisation of certain marketing authorisations, in accordance with a non-binding opinion of the CPMP under Article 12 of that directive, can have the effect of depriving the Member States concerned of their powers, by triggering the application of the arbitration procedure provided for in Article 15a in respect of the adoption of any subsequent decision regarding the suspension or withdrawal of such authorisations.

151.

Furthermore, it must be noted that neither the preamble to Directive 93/39 nor Chapter III of Directive 75/319 includes any general reference among their objectives to the notion, invoked by the Commission, that achieved harmonisation must be maintained. In the scheme of Chapter III of Directive 75/319, that notion is only related to the specific objective of the mutual recognition procedure and has led to the establishment of the arbitration procedures provided for in Articles 15 and 15a of that directive in respect of

the management of marketing authorisations granted within the framework of the mutual recognition procedure.

152.

Accordingly, contrary to the Commission's assertions, it is not possible to interpret Article 15a(1), in conjunction with Article 12 of Directive 75/319, by analogy with Article 15b of that directive, which states that ‘Articles 15 and 15a shall apply by analogy to medicinal products authorised by Member States following an opinion of the [CPMP] given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995’.

153.

The insertion of Article 15b into Chapter III of Directive 75/319 can be accounted for by the special character of the high-technology medicinal products industry which, since 1 January 1995, has been governed by Regulation No 2309/93 establishing the centralised Community procedure. That insertion clearly reflects the intention to make the management of high-technology medicinal products subject to a transitional system of Community arbitration where they have been authorised under the aegis of Directive 87/22, which was repealed with effect from 1 January 1995 by Council Directive 93/41/EEC of 14 June 1993 (OJ 1993 L 214, p. 14). In that respect, it should be recalled that Directive 87/22, as is apparent from the seventh recital in the preamble thereto, had provided for ‘a Community mechanism for concertation, prior to any national decision, with a view to arriving at uniform decisions throughout the Community’. That procedure had been introduced because the ‘procedures for coordinating national decisions’ provided for in Directive 75/319, as amended by Directive 83/570, had not been considered ‘sufficient to open up to high-technology medicinal products the large Community-wide single market they require’ (the third and fifth recitals in the preamble to Directive 87/22).

154.

In those circumstances, no analogy can be drawn between marketing authorisations harmonised under Article 12 of Directive 75/319 and authorisations granted within the framework of Directive 87/22. The latter authorisations were transitionally subject to the scheme established by Articles 15 and 15a of Directive 75/319, in order to ensure the adoption of the common decisions necessary to the development of high-technology medicinal products, after the centralised Community procedure became applicable to that sector.

155.

For all the above reasons, in the scheme of Directive 75/319, the concept of a marketing authorisation granted in accordance with the provisions of Chapter III of that directive, referred to in Article 15a(1), cannot be interpreted as also including authorisations harmonised following consultation of the CPMP under Article 12. The contested decisions therefore have no legal basis and the plea in law alleging the Commission's lack of competence is well founded.

156.

Furthermore, even assuming that the Commission had been competent to adopt the contested decisions, they would nevertheless be flawed on the ground of infringement of Article 11 of Directive 65/65. In that regard, the Court makes the following observations.

2. *Interpretation of the conditions for withdrawal of marketing authorisations of medicinal products laid down in Article 11 of Directive 65/65*

Summary of the arguments of the parties

157.

The applicants submit that the contested decisions infringe Article 11 of Directive 65/65 in three respects. First, they do not respect the rules of evidence laid down in that article. Under Article 11 of Directive 65/65, the burden of proof of lack of therapeutic efficacy or harmfulness of an authorised substance lies with the competent authority. Furthermore, in the case of withdrawal of the marketing authorisation of a medicinal product, the lack of therapeutic efficacy or the harmfulness of that medicinal product in the normal conditions of use must be established beyond doubt, whereas, in the case of an application for authorisation, insufficient substantiation, which covers disagreement between scientists, may be grounds for refusing authorisation. In the present case, the CPMP and the Commission acted on the basis of mere doubts and transferred the burden of proof to the holders of the authorisations of the medicinal products in question.

158.

Second, the applicants in Cases T-74/00 and T-137/00 consider that Article 11 of Directive 65/65 does not provide for an assessment of the benefit/risk balance.

159.

Third, all the applicants submit that the criterion of long-term efficacy, on which the contested decisions are based, is not supported by new scientific

data justifying withdrawal of the marketing authorisations of the medicinal products concerned.

160.

According to the applicants in Cases T-74/00 and T-141/00, that criterion has the effect of favouring long-term medicinal products based on orlistat and sibutramine - two new, recently authorised substances which have not been sufficiently tested. Conversely, amfepramone is a known alternative with no risk of unexpected side effects.

161.

At the hearing, all the applicants also pointed out that following the contested decisions there are now only two substances for the treatment of obesity available on the Community market, orlistat and sibutramine. In view of the seriousness of the medical disorders associated with obesity, the withdrawal of the marketing authorisations of the medicinal products in question here, in breach of the conditions set out in Article 11 of Directive 65/65, thus fails to have regard to the interests related to protection of public health. Moreover, medicinal products containing amfepramone are still authorised in the United States, and the FDA has reauthorised medicinal products containing phentermine.

162.

The Commission submits, first, that in this case, contrary to the applicants' claims, the latest scientific data justify an assessment of the efficacy of the substances in question which differs from that given in the CPMP opinion of 17 July 1996. In its scientific conclusions annexed to the contested decisions, the CPMP expressly stated that the new information, as compared to that available to it in 1996, lay in the changes in the scientific criteria in the treatment of obesity. In that regard, it is clear from the CPMP Note for Guidance that, owing to the chronic nature of the condition, therapeutic efficacy for treating obesity requires a significant and long-term lowering of body weight (of at least one year). That criterion of long-term efficacy is also enshrined in the Scottish guideline of November 1996, the guideline from the Royal College of Physicians of December 1998, and the guideline from the American Society for Clinical Nutrition of 1998, which reflect a broad medical consensus.

163.

The defendant explains that the current scientific □rules□ mentioned in the first part of the CPMP Note for Guidance, which contains general considerations relating to the treatment of obesity, were applicable in the present case. Conversely, the specific, but non-binding, recommendations

relating to clinical trials, which constitute the second part of that Note for Guidance, do not relate to medicinal products which have already received a marketing authorisation, and were not applied in the present case.

164.

Furthermore, the CPMP, in the observations forwarded to the Court by the Commission in reply to written questions, and the expert advising the Commission at the hearing, Ms Saint-Raymond, have confirmed that the criterion of long-term efficacy which was applied in the present case was not based on new scientific information or data. In 1999, the CPMP based its assessment on the scientific data already available to it in 1996, since in the meantime there had been only two new studies, on amfepramone and on phentermine, which, owing to their poor quality, provided no new insights. The new scientific evidence consists in this case of a new consensus in the medical community, expressed in the aforementioned guidelines, which no longer permits the inference that the substances in question are effective. Such changes in the scientific assessment of a form of treatment, leading to its discontinuance, are common. By way of example, streptomycin, which may still have an effect on the Koch bacillus, is no longer used in the treatment of tuberculosis because the medical community recognises the utility of other medicinal products.

165.

Against that background, the Commission accepts that under the first paragraph of Article 11 of Directive 65/65 the onus was on it to prove that the substances in question lacked therapeutic efficacy. In the present case, contrary to the applicants' claims, the Commission did not consider that the applicants were required to demonstrate that the medicinal products containing the substances in question had a long-term effect. The CPMP's conclusion that the substances under consideration lacked efficacy was not based on mere doubts. On the contrary, it is apparent from the CPMP's scientific conclusions, annexed to the contested decisions, that, on the basis of the scientific data at its disposal, the CPMP carried out an analysis of the therapeutic effects of the substances in question, and concluded that they lacked efficacy on the ground that they appear to induce only modest, short-term weight-loss. There have been no controlled studies establishing that those substances have a relevant long-term influence on weight or provide a clinical benefit in the treatment of obesity. At the hearing, the Commission pointed out that it is not the task of the CPMP to carry out scientific studies in order to generate additional data.

166.

The defendant claims that, in the present case, it was impossible to take the view that the short-term effects of the substances under consideration could result in a long-term benefit, because, as the CPMP noted in its scientific conclusions, the initial loss of weight does not prevent rapid weight-regain after treatment is stopped. In Case T-141/00, the defendant notes that recent clinical studies show, by contrast, that other medicinal products intended for the treatment of obesity, such as Xenical (containing orlistat) and Reductil/Zelium/Reduxade (containing sibutramine), can lead to satisfactory weight-loss after treatment for one year, without otherwise causing excessive weight-loss. Treatment with Xenical, which has been authorised in the Community since 29 July 1998, can be continued for two years. It has some minor side effects and there is no risk of dependence. The medicinal product Reductil/Zelium/Reduxade, which have been authorised in Germany since January 1999, can be used for up to 12 months.

167.

In its observations forwarded to the Court by the Commission in reply to a written question from the Court, the CPMP pointed out, however, that it assessed the benefit/risk balance of the anorectics in question solely on the basis of their individual properties and had not taken into account the existence of other substances. In particular, its conclusions were not based on a comparison of the efficacy of those anorectics with the efficacy of medicinal products suitable for long-term use. In that regard, the expert advising the Commission at the hearing confirmed, in reply to a question from the Court, that, when the CPMP issued its final opinions on the substances in question, it was not in possession of comparative studies on those substances, sibutramine and orlistat. The expert stated that, in certain cases, the CPMP requests comparative studies in order to assess the efficacy of a new medicinal product where there is already a medicinal product whose medical usage is well established and which has recognised efficacy and an acceptable level of safety. However, in the present case, it would not have been fair to make such a request in order to re-evaluate established medicinal products which have been authorised for more than 15 or 20 years on the basis of the scientific criteria applicable at the time of authorisation. For a comparative analysis, new studies which meet current standards would have had to be carried out on those medicinal products. Finally, as regards sibutramine, the CPMP explained that following its initial authorisation in Germany in January 1999, that substance was authorised in various Member States by way of the mutual recognition procedure. It was then the subject of a Commission decision of 26 March 2001 under Article 12 of Directive 75/319 which made the continuation of the marketing authorisations of medicinal products containing that substance subject to a number of conditions. A procedure for withdrawal of those authorisations was initiated in March 2002 on the ground of safety, on

the basis of Article 36 of the Code (which reproduces Article 15a of Directive 75/319).

168.

Second, the defendant disputes the contention that medicinal products containing the substances in question are safe in the normal conditions of use. It points out that the risks reported by the CPMP in 1999 had already been taken into consideration in the decision of 9 December 1996.

169.

The inadequate therapeutic efficacy of medicinal products containing the substances in question, in the light of the current scientific criteria, was accordingly weighed, as required under Article 11 of Directive 65/65, against the unchanged but indisputable risks posed by that type of substance, leading the CPMP to conclude that the benefit/risk balance was unfavourable.

Findings of the Court

170.

It is necessary first to clarify the legal rules governing withdrawal of a marketing authorisation before considering the specific issue of whether the contested decisions comply with the conditions for withdrawal laid down in the applicable rules.

The criteria for withdrawal of a marketing authorisation and the rules of evidence

171.

In accordance with Article 21 of Directive 65/65, which provides that a marketing authorisation may not be refused, suspended or revoked except on the grounds set out in that directive, the substantive criteria for withdrawal of a marketing authorisation in order to protect public health are exclusively governed by Article 11 of that directive (see, to that effect, Case C-83/92 *Pierrel and Others* [1993] ECR I-6419, paragraphs 21 to 23).

172.

The first paragraph of Article 11 of Directive 65/65 expressly provides that the competent authorities are to suspend or revoke the marketing authorisation of a medicinal product 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.

173.

The aforementioned conditions for withdrawal of an authorisation must be interpreted in accordance with the general principle, identified in the case-law, that protection of public health must unquestionably take precedence over economic considerations (see, in particular, order in Case C-180/96 R *United Kingdom* v *Commission* [1996] ECR I-3903 paragraph 93, and the judgment in Case C-183/95 *Affish* [1997] ECR I-4315, paragraph 43).

174.

In the context of the grant and management of marketing authorisations of medicinal products, that principle requires, first, the taking account exclusively of considerations relating to the protection of public health; second, the re-evaluation of the benefit/risk balance of a medicinal product where new data give rise to doubts as to its efficacy or safety and, third, the application of rules of evidence in accordance with the precautionary principle, which is implicitly relied on by the Commission (see above, paragraph 165) and is, in particular, the corollary of the principle that the requirements of the protection of public health are to prevail over economic interests.

- Account to be taken exclusively of considerations relating to the protection of health, in decisions on the authorisation of medicinal products

175.

The general principle that precedence must be given to the protection of public health is, as regards medicinal products for human use, expressly enshrined in the first recital in the preamble to Directive 65/65 (recital 2 in the preamble to the Code), which states that □the primary purpose□ of any rules concerning the production and distribution of medicinal products □must be to safeguard public health□, and in the third recital in the preamble to Directive 93/39, which provides that □in the interest of public health and of the consumer of medicinal products, it is necessary that decisions on the authorisation to place medicinal products on the market be exclusively based on the criteria of quality, safety and efficacy ... extensively harmonised by ... Directive 65/65 ...□.

176.

Those provisions confirm that only requirements related to the protection of public health must be taken into consideration when a marketing authorisation is granted under Article 5 of Directive 65/65 (Article 26 of the Code), when such an authorisation is renewed under Article 10(1) of that directive (Article 24 of the Code), and in the management of marketing authorisations in accordance with Article 11 of that directive (Article 116 of the Code).

177.

In particular, in view of the precedence thereby accorded to the protection of public health, where, on the basis of the progress of scientific knowledge and new data collected in particular in the context of pharmacovigilance, the competent authority proves to the requisite legal standard that a medicinal product no longer meets one of the criteria set out in Article 11 of the directive, the holder of the marketing authorisation of that medicinal product, which is valid for five years and renewable for five-year periods pursuant to Article 10 of Directive 65/65, may not claim that he is entitled, by virtue of the principle of legal certainty, to specific protection of his interests during the period of the authorisation's validity.

- Re-evaluation of the benefit/risk balance in the light of new data

178.

It should be noted 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. As the seventh recital in the preamble to Directive 75/318 states, the concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge. That provision has, moreover, been reproduced as recital 7 in the preamble to the Code, which clearly confirms that, contrary to the applicants' claims, the requirement to carry out an evaluation of the benefit/risk balance of a medicinal product does not apply exclusively to the grant of a marketing authorisation but applies in particular to the procedure for withdrawal of such an authorisation. Furthermore, in the introduction of the Annex to Directive 75/318, the legislature states essentially that after the marketing authorisation has been issued any new data or information must be submitted to the competent authorities in order to monitor the benefit/risk assessment.

179.

Against that background, contrary to the applicants' arguments, the proposal submitted by the Commission on 26 November 2001 for a directive amending Directive 2001/83/EC on the Code (COM (2001) 404 final), which seeks specific reference in Article 116 of the Code (corresponding to Article 11 of Directive 65/65) to the assessment of the risk-benefit balance, merely makes explicit the conditions set out in that article, in the version currently in force.

180.

It follows, in particular, that the reasons which have led a competent authority to maintain a marketing authorisation of a medicinal product notwithstanding certain harmful effects may cease to apply if that authority finds that the benefits justifying such an authorisation, that is to say the existence of a therapeutic effect, are no longer present and, consequently, the medicinal product under consideration no longer has a favourable benefit/risk balance (cf. order in *Commission* v *Trenker*, cited above, paragraph 67).

- The rules of evidence in relation to the precautionary principle

181.

In addition, where there is scientific uncertainty, it is for the competent authority to assess the medicinal product in question in accordance with the precautionary principle. It is therefore appropriate to recall the origin and content of that principle before explaining its effect on the rules of evidence in connection with the system of prior authorisation of medicinal products.

182.

As regards environmental matters, the precautionary principle is expressly enshrined in Article 174(2) EC, which establishes the binding nature of that principle. Furthermore, Article 174(1) includes protecting human health among the objectives of Community policy on the environment.

183.

Therefore, although the precautionary principle is mentioned in the Treaty only in connection with environmental policy, it is broader in scope. It is intended to be applied in order to ensure a high level of protection of health, consumer safety and the environment in all the Community's spheres of activity. In particular, Article 3(p) EC includes 'a contribution to the attainment of a high level of health protection' among the policies and activities of the Community. Similarly, Article 153 EC refers to a high level of consumer protection and Article 174(2) EC assigns a high level of protection to Community policy on the environment. Moreover, the requirements relating to that high level of protection of the environment and human health are expressly integrated into the definition and implementation of all Community policies and activities under Article 6 EC and Article 152(1) EC respectively.

184.

It follows that the precautionary principle can be defined as a general principle of Community law requiring the competent authorities to take appropriate measures to prevent specific potential risks to public health, safety and the environment, by giving precedence to the requirements related to the protection of those interests over economic interests. Since the

Community institutions are responsible, in all their spheres of activity, for the protection of public health, safety and the environment, the precautionary principle can be regarded as an autonomous principle stemming from the abovementioned Treaty provisions.

185.

It is settled case-law that, in the field of public health, the precautionary principle implies that where there is uncertainty as to the existence or extent of risks to human health, the institutions may take precautionary measures without having to wait until the reality and seriousness of those risks become fully apparent (Case C-180/96 *United Kingdom* v *Commission* [1998] ECR I-2265, paragraph 99, and Case T-199/96 *Bergaderm and Goupil* v *Commission* [1998] ECR II-2805, paragraph 66). Prior to the enshrinement in case-law of the precautionary principle, on the basis of the Treaty provisions, that principle was implicitly applied in the review of proportionality (see, to that effect, order in Case C-180/96 R *United Kingdom* v *Commission*, paragraphs 73 to 78, and the order of the President of the Court of First Instance in Case T-76/96 R *National Farmers' Union and Others* v *Commission*[1996] ECR II-815, paragraphs 82 to 93, in particular paragraph 89).

186.

Where scientific evaluation does not make it possible to determine the existence of a risk with sufficient certainty, whether to have recourse to the precautionary principle depends as a general rule on the level of protection chosen by the competent authority in the exercise of its discretion (on the distinction between scientific advice, on the one hand, and that discretionary assessment of the competent authority, on the other, see the judgment in Case C-405/92 *Mondiet* [1993] ECR I-6133, paragraph 31, and the Opinion of Advocate General Gulmann in that case, point 28). That choice must, however, comply with the principle that the protection of public health, safety and the environment is to take precedence over economic interests, as well as with the principles of proportionality and non-discrimination.

187.

In the Community system of prior authorisation of medicinal products the competent authority, when considering an application for authorisation of a medicinal product, in principle exercises its discretion in weighing up the benefits and risks of that medicinal product - reserving the right subsequently to revise its assessment of that benefit/risk balance in the light of new scientific data.

188.

As regards, more specifically, the rules of evidence applicable to that system, it is for the undertaking seeking marketing authorisation of a medicinal product to prove, first, the efficacy of the medicinal product and, second, its safety, that proof being based, in particular, on trials in accordance with the provisions of Directive 75/318.

189.

Subsequently, when an application for renewal of an authorisation, the validity of which is limited to five years under Article 10(1) of Directive 65/65, is considered, the assessment of the medicinal product is to be carried out, according to that article, on the basis of the details of pharmacovigilance data and other information relevant to the monitoring of medicinal products.

190.

Furthermore, it is clear from Article 10(2) of that directive that it is only [i]n exceptional circumstances, and following consultation with the applicant that an authorisation may be made subject to certain specific obligations, including, in particular, the carrying out of further studies following the granting of authorisation. Those exceptional decisions may be adopted only for objective and verifiable reasons, referred to in Part 4(G) of the Annex to Directive 75/318, that is in particular where in the present state of scientific knowledge the applicant cannot provide comprehensive information on the efficacy and safety of the medicinal product in question under normal conditions of use.

191.

In that system, save in the special situation provided for in Article 10(2) of Directive 65/65, the holder of the marketing authorisation of a medicinal product is not required to provide evidence of the efficacy and/or safety of that medicinal product during the period of that authorisation's validity. As the Commission acknowledges, the onus is indisputably on the competent authority to prove that just one of the conditions for withdrawal, variation or suspension of a marketing authorisation, which are set out in Article 11 of Directive 65/65, is met. Contrary to the applicants' contentions, acceptance that in cases of scientific uncertainty reasonable doubts as to the efficacy or safety of a medicinal product are capable of justifying a precautionary measure cannot be treated as equivalent to a reversal of the burden of proof.

192.

The precautionary principle requires the suspension or withdrawal of a marketing authorisation where new data give rise to serious doubts as to either the safety or the efficacy of the medicinal product in question and those doubts lead to an unfavourable assessment of the benefit/risk balance of that

medicinal product (see above, paragraph 178). Against that background, the competent authority need do no more than provide, in accordance with the general rules of evidence, solid and convincing evidence which, while not resolving the scientific uncertainty, may reasonably raise doubts as to the safety and/or efficacy of the medicinal product.

193.

In addition, the passages in the legislation which highlight the relative nature of the assessment of a medicinal product, in particular the seventh and eighth recitals in the preamble to Directive 75/318, refer to the progress of scientific knowledge and to new discoveries. It is also clear from the introduction of the Annex to Directive 75/318 that the benefit/risk balance is to be assessed continuously on the basis of any new information or data submitted to the competent authorities.

194.

Against that background, leaving aside the exceptional situation in which the competent authority makes a detailed acknowledgement that it had incorrectly assessed a medicinal product when taking the decision to grant or, as the case may be, maintain or renew the authorisation, the withdrawal of a marketing authorisation must in principle be regarded as justified only where a new potential risk or the lack of efficacy is substantiated by new, objective, scientific and/or medical data or information. In particular, it is entirely logical that the application of a new assessment criterion, which reflects a current consensus in the medical community, is justifiable during the period of the authorisation's validity only if that development is based on new data or information.

195.

Those requirements are clearly compatible with the need to ensure the highest level of health protection in the management of marketing authorisations of medicinal products. Before obtaining the marketing authorisation of a medicinal product, the applicant is required to prove that that medicinal product has a favourable benefit/risk balance. In addition, the validity of the authorisation is in principle limited to a renewable period of five years. In those circumstances, the system of prior authorisation allows the presumption that, during that period, in the absence of any solid evidence to the contrary, the medicinal product in question has a favourable benefit/risk balance, subject always to the possibility of suspending the authorisation in cases of emergency. Where there is no such evidence, the need not to reduce the range of medicinal products available for the treatment of a particular disorder argues in favour of keeping the medicinal product on the market so that, in every case, the most appropriate medicinal product may be prescribed.

Review of the contested decisions

196.

Before considering the lawfulness of the contested decisions, it is appropriate at the outset to define the scope of the Court's review.

197.

The procedure established in Article 15a of Directive 75/319 is characterised by the vital role accorded to an objective and detailed scientific assessment by the CPMP of the substances in question. Although the CPMP's opinion does not bind the Commission, it is none the less extremely important so that any unlawfulness of that opinion must be regarded as a breach of essential procedural requirements rendering the Commission's decision unlawful.

198.

Since the Commission is not in a position to carry out scientific assessments of the efficacy and/or harmfulness of a medicinal product, the aim of the mandatory consultation of the CPMP is to provide the Commission with the evidence of scientific assessment which is essential for it to be able to determine, in full knowledge of the facts, the appropriate measures to ensure a high level of public health protection (see, by analogy, on cosmetic products, Case C-212/91 *Angelopharm* [1994] ECR I-171, paragraphs 31, 32 and 38, and *Bergaderm and Goupil* v *Commission*, cited above, paragraph 64).

199.

Against that background, for the purposes of assessing the lawfulness of a Commission decision based on Article 15a of Directive 75/319, the Community judicature may be called upon to review, first, the formal legality of the CPMP's scientific opinion and, second, the Commission's exercise of its discretion.

200.

As regards the CPMP opinion, the Court cannot substitute its own assessment for that of the CPMP. It is only the proper functioning of the CPMP, the internal consistency of the opinion and the statement of reasons contained therein which are subject to judicial review. As regards the last aspect, the Court is empowered only to examine whether the opinion contains a statement of reasons from which it is possible to ascertain the considerations on which the opinion is based, and whether it establishes a comprehensible link between the medical and/or scientific findings and its conclusions. In that respect, in its opinion the CPMP is obliged to refer to the main reports and scientific expert opinions on which it relies and to explain, in the event of a significant discrepancy, the reasons why it has departed from

the conclusions of the reports or expert opinions supplied by the undertakings concerned. That obligation is particularly strict in cases of scientific uncertainty. By guaranteeing that the consultation of the CPMP is *inter partes* and transparent, it ensures that the substance in question has undergone a detailed and objective scientific assessment, based on a comparison of the most representative scientific opinions with the scientific arguments advanced by the pharmaceutical laboratories concerned (cf. Case T-27/98 *Nardone* v *Commission* [1999] ECR-SC I-A-267; ECR-SC II-1293, paragraphs 30 and 88).

201.

As regards the Commission's exercise of its discretion, it should be noted that it is settled case-law that where a Community institution is called upon to make complex assessments it enjoys a wide measure of discretion, the exercise of which is subject to a judicial review restricted to verifying that the measure in question is not vitiated by a manifest error or a misuse of powers and that the competent authority did not clearly exceed the bounds of its discretion (*Mondiet*, cited above, paragraph 32; *United Kingdom* v *Commission*, cited above, paragraph 97, and Case C-120/97 *Upjohn* [1999] ECR I-223, paragraph 34).

202.

In the contested decisions, the Commission justifies the withdrawal of the marketing authorisations of the medicinal products in question by referring, in Article 2 of the operative part of those decisions, to the scientific conclusions of the CPMP attached to its final opinions, which are annexed to those decisions.

203.

It is clear from those scientific conclusions that the contested decisions are based on a negative assessment of the benefit/risk balance of the substances in question, following a reevaluation of their efficacy on the basis of a criterion different from that applied in the CPMP opinions of 17 July 1996 on the same substances, in the light of its assessment report of 18 July 1996 (see above, paragraphs 23 and 24). By contrast, as regards safety, it is evident from the CPMP's scientific conclusions, and confirmed by the Commission's statements in these proceedings, that the CPMP considered in the present case that the risks posed by the substances in question had not changed since 1996. In mentioning in its scientific conclusions on amfepramone and on phentermine that the risk of cardiac valve disorders could not be ruled out, the CPMP was merely stating that no evidence could be supplied to show that there was no such risk. Moreover, its scientific conclusions explicitly stated that, for all the substances under consideration, there was no solid evidence to justify an

assumption that their use increases the risk of cardiac valve disorders. In addition, when carrying out its assessment of the benefit/risk balance of the substances in question, the CPMP weighed their purported lack of efficacy against only those risks which had already been taken into consideration in 1996.

204.

As regards the efficacy of those substances, the Court finds that even in 1996 the CPMP stated that the long-term efficacy of the substances under consideration had not been proven, that no significant data was available as to the effects of those substances on morbidity and mortality, and that weight-regain occurred immediately after discontinuation of the pharmacological treatment. It did however accept that the weight-loss of 2 to 5 kg on average, achieved after short-term treatment, was evidence of the efficacy of those substances, an opinion endorsed by the Commission in its decision of 9 December 1996. In the present case the CPMP opinions of 31 August 1999 and the contested decisions, while revising that evaluation, are based on medical and scientific data in respect of the therapeutic effects of the substances in question, which are strictly identical to those taken into consideration in 1996, as the Commission has moreover confirmed.

205.

In that regard, it must however be observed that, in the present case, neither the CPMP, in its final opinions, nor the Commission, in the contested decisions, claims to have relied on an assessment of the acceptable risk in respect of the short-term therapeutic effects of the medicinal products in question which was different from the assessment of 1996. Accordingly the Commission has not at any point called into question the choice it made in 1996 to maintain the marketing authorisations of those medicinal products and merely to amend the summaries of product characteristics. On the contrary, the Commission maintains that that choice was justified, at that time.

206.

In justification of the adoption of measures fundamentally different from those adopted in 1996, the Commission refers only to the application of the criterion of the long-term efficacy of the medicinal products in the treatment of obesity.

207.

It is important to note that that criterion is not a legal criterion which supplements or modifies the efficacy criterion set out in Article 11 of Directive

65/65, but a purely scientific criterion relating specifically to the assessment of the medicinal products in the treatment of obesity.

208.

The Commission has also confirmed that the possible existence of substitute substances - which, having regard to the data available in 1999, could, in appropriate cases, have had a more favourable benefit/risk balance - was not taken into consideration by the CPMP when it evaluated the substances in question, which were the subject of strictly individual assessments (see above, paragraph 167). In that respect, it should be noted that although two new substances designed for the treatment of obesity and suitable for long-term use were referred to in both a preparatory report common to the three procedures and the Commission's defence in Case T-141/00 (see above, paragraphs 33 and 166), they were not mentioned by either the CPMP in its opinions or the Commission in the contested decisions. In those circumstances, none of the evidence before the Court supports the presumption that the existence of those substances had any effect on the application of the criterion of long-term efficacy in the present case.

209.

In this case, an examination of, in particular, the successive preparatory reports drawn up in the course of the administrative procedure relating to amfepramone confirms that the change in the CPMP's position as regards the evaluation of the efficacy of the substances in question followed the entry into force, in June 1998, of the Note for Guidance adopted by the CPMP in November 1997. Accordingly, as regards, for example, amfepramone, the pharmacovigilance working party's report of May 1998 and the Picon/Abadie Report of 4 June 1998 stated that the efficacy of that substance in the treatment of obesity had not changed. It was the questionnaire sent to the undertakings concerned on 27 July 1998 which made the first reference to the evaluation of the benefit/risk balance of the substances in question in the light of the CPMP Note for Guidance. The Castot/Fosset Martinetti/Saint-Raymond Report, drawn up in April 1999, found that amfepramone lacked efficacy on the ground that the duration of treatment with medicinal products containing that substance was limited to three months, which, according to the report, was incompatible with the current guidelines recommending long-term treatment. Finally, in a discussion paper of 12 April 1999, Professor Winkler relied on the CPMP Note for Guidance to refute the argument put forward by the undertakings concerned that there was no new data on the efficacy or safety of the substances concerned which was capable of justifying a departure from the CPMP opinion of 1996 on the same substances. Professor Winkler asserted that in 1999 there was a general consensus that therapeutic efficacy in the treatment of obesity required a significant and lasting loss of weight (see above, paragraphs 28 to 30, 32 and 33).

Furthermore, the referral to the CPMP by Austria on 31 August 1998 in respect of, *inter alia*, clobenzorex and the other substances in question in Cases T-83/00 to T-85/00 (see above, paragraph 61) mentions the guidelines among the recent developments concerning the efficacy of anorectics.

210.

Furthermore, it is common ground that the use, in the present case, of a criterion for assessing the efficacy of the substances in question which differs from that applied in 1996 is based solely on the purported development of a □consensus□ within the medical community on the criterion for assessing the efficacy of medicinal products in the treatment of obesity, as confirmed by the Commission on numerous occasions both in its written observations and at the hearing (see above, paragraphs 162 and 164). That new consensus is purportedly reflected in the CPMP Note for Guidance and the national guidelines, which were cited in the CPMP's scientific conclusions. Yet, neither those documents nor the scientific conclusions of the CPMP make any reference to new scientific data or information which were not available in 1996 and would explain the development of that consensus.

211.

In those circumstances, the Court finds that mere changes in a scientific criterion or, in more concrete terms, in good clinical practices - that is to say, therapeutic practices considered to be the most appropriate in the light of current scientific knowledge -, even if based on a □consensus□ in the medical community, cannot on their own justify the withdrawal of a marketing authorisation of a medicinal product under Article 11 of Directive 65/65 where, as has been held above (paragraphs 192 to 195), those changes are not based on new scientific data or information.

212.

Moreover, the Court in any event finds that neither the CPMP Note for Guidance nor the national guidelines referred to in the CPMP opinions of 31 August 1999 establishes any new criterion for assessing the efficacy of a medicinal product in the treatment of obesity.

213.

As submitted by the applicants, the CPMP expressly stated in its Note for Guidance that that note was to be read □in conjunction with the Annex [to] Directive 75/318□ and that it accordingly related to the clinical trials whose results must accompany the initial applications for marketing authorisations of medicinal products used for weight control, which are submitted under Article 4 of Directive 65/65. As the Commission acknowledges, only the

general considerations on the treatment of obesity set out in that Note for Guidance are thus of relevance to the present case.

214.

In those general considerations, the CPMP does not refer to a criterion for efficacy which differs from that applied in 1996. It states that obesity is a chronic clinical condition which usually requires long-term therapy to induce and maintain weight-loss. It adds that [t]he treatment of obesity should be clinically relevant, aiming for prolonged and maintained weight loss in order to decrease associated morbidity and mortality. That passage, which, according to the written observations submitted by the Commission, after consulting the CPMP, in reply to a written question from the Court, confirms that the guidelines establishing the criterion of long-term efficacy applied in the present case, does not contain any innovation when compared with the passage in the assessment report of 18 July 1996 in which the CPMP had already stated:

[t]he objective of the treatment of obesity must be to reach a clinically relevant and maintained weight loss, which is likely to decrease cardio-vascular risk factors, in order to prevent morbidity and mortality.

215.

In fact, in its Note for Guidance the CPMP summarises the various non-pharmacological and pharmacological treatment options (centrally-acting, amphetamine-like or serotonergic anorectics; orlistat, which was being developed at the time the CPMP Note for Guidance was adopted). The extract cited above thus refers to all the complementary therapies used in the treatment of obesity. In the introduction to its Note for Guidance, the CPMP notes, in particular, that pharmacological treatment is considered only as an adjunct to dietary measures. As regards, more specifically, the amphetamine-like anorectics, which include the substances in question in this case, it notes that their stimulant or euphoric effect has been associated with potential for abuse. More generally, as regards centrally- acting anorectics it also reports that it has been shown that a duration of treatment greater than three months and a BMI of greater than 30 kg/m² increase the risk of developing pulmonary artery hypertension. It does not however conclude that the fact that those medicinal products cannot be used continuously for longer than a limited period means that they lack efficacy.

216.

It must be stated that the other three extracts from the CPMP Note for Guidance cited by the Commission - in reply to a question from the Court which sought to identify the specific passages in that document, and in the

other three guidelines relied on in the CPMP's scientific conclusions, which refer to the criterion of long-term efficacy as applied in the present case - do not lay down the criterion applied in the present case. By stating, under the heading Measurement of Weight Loss, first, that [a] further illustration of the size of the treatment effect should be provided by looking at the proportions of responders in the various treatment arms - where response is more than 10% weight loss at the end of a 12 month period and, second, that [t]he maintenance of weight loss or the prevention of weight regain, after the plateau in weight [often observed after five to six months of treatment] has been reached, could also be considered as an efficacy criterion, the CPMP was clearly simply identifying a number of criteria for assessing the efficacy of a medicinal product in the treatment of obesity without conferring on them any exclusivity. Under that same heading, it also noted, at the outset, that [r]elevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight and that [d]emonstration of a significant degree of weight loss of at least 10% of baseline weight ... is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Finally, the CPMP was expressly referring to the clinical trials which must be carried out for the purpose of granting a new marketing authorisation for a medicinal product when, under the heading Strategy and design of clinical trials, it stated: [a]t present, trials documenting the effect of treatment for at least one year are required but a longer prospective study would be required by an applicant intending to demonstrate the effect of weight loss on morbidity and mortality. Contrary to the Commission's contentions, that last recommendation is thus of absolutely no relevance to the present case.

217.

The aim of the three national guidelines referred to in the CPMP opinions of 31 August 1999 is to present good clinical practices in the treatment of obesity, in the light of the available evidence. The passages in those guidelines cited by the Commission in reply to the aforementioned question from the Court do not however lend more support to the criterion of the long-term efficacy of the medicinal products which was applied in the present case. The extracts from the Royal College of Physicians' Guideline relied on by the defendant stress the chronic nature of obesity and state that [t]reatment programmes must be for the longer term, possible lifelong, and include measures to prevent relapse. Such programmes clearly include the entire range of therapies used in the treatment of that disorder. They may include pharmacological treatment which, however, according to the decision of 9 December 1996, is only to be used as second line adjunctive treatment.

218.

Similarly, the passages from the Guideline of the American Society for Clinical Nutrition cited by the Commission unquestionably refer to the overall treatment of obesity and do not specifically relate to the assessment of the efficacy of the medicinal products. That guideline also points out that pharmacotherapy is only a second line adjunctive treatment.

219.

Finally, the definition of ‘weight maintenance’ in the Scottish Guideline of November 1996, as ‘long term, i.e., > 2 year, maintenance of body weight achieved following a period of weight loss…’, relates in general terms to all the therapies employed in the treatment of obesity. It does not permit the inference that weight maintenance for such a period constitutes the criterion for assessing the efficacy of medicinal products in the treatment of obesity. In addition, under the heading ‘Drug selection and duration of treatment’, which addresses the long-term use of the medicinal products, the guideline states that many earlier medicinal products were misused, that several had amphetamine-like actions which led to dependence, and that ‘[t]he Guideline Development Group considers that these drugs should not be used until separately evaluated with prolonged (> 1 year) use’. Put back into its context, that passage, relied on by the Commission, thus relates more specifically to the evaluation of the side-effects of the substances under consideration when used long-term. Earlier in the guideline it was stated under the same heading that the guideline development group considered that the restriction of pharmacotherapy to a maximum of three months was inappropriate and that continued therapy might be warranted, although it was expressly noted that that question was open to debate. It is therefore not possible to infer from that guideline the existence of the purported medical consensus in favour of the criterion of long-term efficacy in the form applied in the present case. Moreover, the guideline does not refer to any new data or information, not yet available in 1996, to justify the inappropriateness of pharmacological treatment limited to a term of three months.

220.

In those circumstances, given the lack of any new scientific data or information relating to assessment of the efficacy of the substances in question, Article 11 of Directive 65/65 precluded the competent authority from revising the positive assessment of the efficacy of the substances under consideration, which had been issued in 1996. It follows that, on any view, the contested decisions are in breach of the provisions of that article.

221.

The contested decisions must be annulled in so far as they relate to the medicinal products marketed by the applicants.

Costs

222.

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 applicants, be ordered to pay all the costs including those relating to the interlocutory proceedings.

On those grounds,

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

hereby:

1. Annuls the Commission Decisions of 9 March 2000 (C(2000) 452, C(2000) 453 and C(2000) 608) in so far as they relate to the medicinal products marketed by the applicants;

2. Orders the Commission to pay all the costs, including those incurred in the interlocutory proceedings.

Delivered in open court in Luxembourg on 26 November 2002.

H. Jung

R.M. Moura Ramos

Registrar

President