JUDGMENT OF THE GENERAL COURT (Fifth Chamber)

9 September 2010 *

In Case T-74/08,

Now Pharm AG, established in Luxembourg (Luxembourg), represented initially by C. Kaletta and I.-J. Tegebauer, and subsequently by C. Kaletta, lawyers,

applicant,

v

European Commission, represented by B. Schima and M. Šimerdová, acting as Agents,

defendant,

* Language of the case: German.

APPLICATION for annulment of Commission Decision C(2007) 6132 of 4 December 2007 refusing the designation of 'Chelidonii radix special liquid extract' as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ 2000 L 18, p. 1),

THE GENERAL COURT (Fifth Chamber),

composed of M. Vilaras, President, M. Prek (Rapporteur) and V.M. Ciucă, Judges,

Registrar: K. Andová, Administrator,

having regard to the written procedure and further to the hearing on 28 April 2010,

gives the following

Judgment

Legal context

1 In order to provide effective treatments for patients affected by rare diseases in the European Community, the European Parliament and the Council adopted Regulation

(EC) No 141/2000 of 16 December 1999 on orphan medicinal products (OJ 2000 L 18, p. 1). That regulation, which entered into force on 22 January 2000, introduces a system of initiatives to encourage pharmaceutical companies to invest in research, development and bringing to the market of medicinal products intended for the diagnosis, prevention or treatment of rare diseases.

2 Article 3(1) of Regulation No 141/2000 provides as follows:

'A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or

that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.'

3 The designation procedure laid down in Article 5 of Regulation No 141/2000, in the version applicable to the facts in the present case, is as follows:

'1. In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the [European Medicines Agency] at any stage of the development of the medicinal product before the application for marketing authorisation is made.

2. The application shall be accompanied by the following particulars and documents:

(a) name or corporate name and permanent address of the sponsor;

(b) active ingredients of the medicinal product;

(c) proposed therapeutic indication;

(d) justification that the criteria laid down in Article 3(1) are met and a description of the stage of development, including the indications expected.

3. The Commission shall, in consultation with the Member States, the Agency and interested parties, draw up detailed guidelines on the required format and content of applications for designation.

4. The Agency shall verify the validity of the application and prepare a summary report to the [Committee for Orphan Medicinal Products]. Where appropriate, it may request the sponsor to supplement the particulars and documents accompanying the application.

5. The Agency shall ensure that an opinion is given by the Committee within 90 days of the receipt of a valid application.

6. When preparing its opinion, the Committee shall use its best endeavours to reach a consensus. If such a consensus cannot be reached, the opinion shall be adopted by a majority of two thirds of the members of the Committee. The opinion may be obtained by written procedure.

7. Where the opinion of the Committee is that the application does not satisfy the criteria set out in Article 3(1), the Agency shall forthwith inform the sponsor. Within 90 days of receipt of the opinion, the sponsor may submit detailed grounds for appeal, which the Agency shall refer to the Committee. The Committee shall consider whether its opinion should be revised at the following meeting.

8. The Agency shall forthwith forward the final opinion of the Committee to the Commission, which shall adopt a decision within 30 days of receipt of the opinion. Where, in exceptional circumstances, the draft decision is not in accordance with the opinion of the Committee, the decision shall be adopted in accordance with the procedure laid down in Article 73 of [Council] Regulation (EEC) No 2309/93 [of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (OJ 1993 L 214, p. 1)]. The decision shall be notified to the sponsor and communicated to the Agency and to the competent authorities of the Member States.

9. The designated medicinal product shall be entered in the Community Register of Orphan Medicinal Products.

…'

4 Article 3(2) of Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority' (OJ 2000 L 103, p. 5) provides:

'For the purposes of the implementation of Article 3 of Regulation (EC) No 141/2000 on orphan medicinal products, the following definition shall apply:

— "significant benefit" means a clinically relevant advantage or a major contribution to patient care.'

5 The Commission of the European Communities also adopted a Communication on Regulation (EC) No 141/2000 (OJ 2003 C 178, p. 2) point A 4 of which reads as follows:

'…

Significant benefit is defined in … Regulation … No 847/2000 as "a clinically relevant advantage or a major contribution to patient care". The applicant is required to establish significant benefit compared with an existing authorised medicinal product or method at the time of designation. As there may be little or no clinical experience with the orphan medicinal product in question, the justification for significant benefit is likely to be made on assumptions of benefit by the applicant. In all cases the Committee [for] Orphan Medicinal Products (COMP) is required to assess whether or not these assumptions are supported by available data/evidence supplied by the applicant.

In all cases the assumption of significant benefit must be justified by the applicant through the provision of evidence/data, which must be considered in the light of the particular characteristics of the condition and the existing methods. …'

6 Also, Article 10(1) of the Rules of Procedure of the Committee for Orphan Medicinal Products of the European Medicines Agency (EMA) ('the Committee') (COMP/8212/00 Rev 2) of 8 December 2004 provides:

'When necessary, the Committee and its working groups may avail themselves of the services of experts in specific scientific or technical fields. Such experts shall be included in the European Experts list.'

7 Lastly, Article 11(2) and (3) of the Committee's Rules of Procedure provide:

'2. The members of the Committee, members of working groups, and experts mentioned in various articles of the present Rules of Procedure, shall not have any direct interests in the pharmaceutical industry which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner, and shall make an annual declaration of their financial interests. All indirect interests which could relate to the pharmaceutical industry shall be entered in a register held by the Agency which is accessible to the public, on request. In addition, the Declarations of Interest of the members of the Committee shall be made available on the Agency's website.

3. Members of the Committee and working groups (and experts attending these meetings) shall declare at the beginning of each meeting any specific interests, which could be considered to be prejudicial to their independence with respect to the points of the agenda. These declarations shall be made available to the public.'

Background to the dispute

8 The applicant, Now Pharm AG, has developed a medicinal product, 'Chelidonii radix special liquid extract' ('Ukrain'), for the treatment of pancreatic cancer. It describes the product as a substance extracted from chelidonium which is administered intravenously; it accumulates in the primary tumour and in metastases in a few minutes and becomes fluorescent when scanned with a laser, showing clearly the difference between diseased and healthy tissue; it destroys cancer cells without damaging healthy tissue.

9 The applicant has obtained authorisation to place Ukrain on the market in a number of States outside the European Union. However, it states that it was refused such authorisation in Austria in 2002 on the basis of a report by an expert, Professor H. W.

10 On 6 February 2007 the applicant submitted an application to the EMA for designation of Ukrain as an orphan medicinal product.

11 On 31 May 2007 the Committee delivered an unfavourable opinion under Article 5(6) of Regulation No 141/2000 and recommended that Ukrain should be refused designation as an orphan medicinal product. It found that Ukrain did not meet the conditions laid down in Article 3(1)(a) of Regulation No 141/2000 and that it had not been established in pursuance of Article 3(1)(b) of that regulation that Ukrain was of significant benefit to those affected by the condition in question, for which a satisfactory method of treatment had been authorised by the Community. On 25 June 2007 the applicant brought an appeal against that opinion under Article 5(7) of Regulation No 141/2000. On 6 September 2007 it submitted detailed grounds for that appeal.

12 On 10 October 2007 the Committee adopted an unfavourable final opinion under Article 5(8) of Regulation No 141/2000. The Committee found that Ukrain met the conditions laid down in Article 3(1)(a) of Regulation No 141/2000 but that the applicant had not established, in pursuance of Article 3(1)(b) of Regulation No 141/2000, that Ukrain was of significant benefit to those affected by the condition in question, in view of the satisfactory methods for treating the disease already existing. The Committee therefore upheld the unfavourable opinion of 31 May 2007 and recommended that the designation of Ukrain as an orphan medicinal product for the treatment of pancreatic cancer should be refused.

13 By decision of 4 December 2007 ('the contested decision'), notified to the applicant on 5 December 2007, the Commission followed the EMA's recommendation made in its opinion of 10 October 2007 and rejected the application for designation of Ukrain as an orphan medicinal product for the treatment of pancreatic cancer.

Procedure and forms of order sought

14 By application lodged at the Registry of the Court on 6 February 2008, the applicant brought the present action.

15 On hearing the report of the Judge-Rapporteur, the General Court (Fifth Chamber) decided to open the oral procedure.

16 At the hearing on 28 April 2010, the parties presented oral argument and replied to questions put by the Court.

17 The applicant claims that the Court should:

— annul the contested decision;

— hold that the Commission should take a new decision in relation to the applicant's application of 6 February 2007, taking into consideration the Court's view of the law;

— order the Commission to pay the costs.

18 The Commission contends that the Court should:

— dismiss the application as unfounded;

— order the applicant to pay the costs.

Law

The claim that the Court should hold that the Commission should take a new decision in relation to the applicant's application of 6 February 2007, taking into consideration the Court's view of the law

19 Since it is not for the Community judicature to issue directions to Community institutions when exercising the jurisdiction to annul acts conferred on it by the Treaty, such a head of claim is inadmissible.

The claim for annulment

20 The applicant raises three pleas in law supporting its claim for annulment. In its first plea, the applicant complains that the Commission infringed Article 3(1) of Regulation No 141/2000. The second plea concerns alleged lack of qualification and lack of impartiality on the part of one of the experts consulted by the Committee. Lastly, in its third plea, the applicant claims that the contested decision contains manifest errors of assessment.

First plea: infringement of Article 3(1) of Regulation No 141/2000

— Arguments of the parties

21 The applicant submits that the Commission infringed Article 3(1) of Regulation No 141/2000, which lays down the conditions for obtaining the designation of a medicinal product as an orphan medicinal product.

22 In the first place, the applicant maintains that, in reaching its conclusion that Ukrain did not offer significant benefit to those affected by pancreatic cancer as compared with methods of treatment currently authorised, the Commission in fact based its assessment on a criterion provided for in Article 8(3)(c) of Regulation No 141/2000, namely clinical superiority. The applicant points out, however, that that criterion is

not required to be met unless the sponsor of an orphan medicinal product is applying for authorisation to market that product. It considers that, in order to obtain designation of Ukrain as an orphan medicinal product, it was sufficient for it to establish that the medicinal product was of significant benefit and that there was no need to establish its clinical superiority.

23 In particular, the applicant submits that the conditions laid down in Article 3(1)(b) of Regulation No 141/2000, including that of significant benefit, were met and that Ukrain should therefore have been designated as an orphan medicinal product. It states that Ukrain is intended to treat a rare condition, namely pancreatic cancer, and also that the product is in itself of significant benefit since it is toxic only for cancer cells and not for healthy cells, it prolongs the lives of those affected by pancreatic cancer and it is a last resort for patients for whom the effects of the authorised treatment are too toxic.

24 In support of its considerations, the applicant states that it submitted a number of preclinical studies and four clinical studies (Zemskov, 2002, Gansauge, 2002, Aschhoff, 2003, and Gansauge, 2007) to the Committee at the time of the application for designation as an orphan medicinal product, in the reasoning submitted in September 2007 in support of the action it brought in June 2007, and when it submitted its observations at a meeting at the EMA in October 2007. Those various studies helped to clarify the details of the mechanism of action of Ukrain and provide grounds for concluding that no other substance possesses properties that are as beneficial in the treatment of the cancer.

25 In that connection, the applicant disputes first of all one study (Panzer, 2000) which concluded that Ukrain was also toxic for normal cells. It maintains, first, that the

authors of that study did not explain the manifest inconsistencies between that study and previous studies and, secondly, that no subsequent study was conducted confirming that conclusion.

26 The applicant also observes that the 'pilot' clinical study funded by a German university, Gansauge (2007), showed that, for pancreatic cancer, Ukrain was not just effective *in vitro* but also offered significant clinical benefits as regards efficacy and tolerance in comparison with conventional treatments. Combined with a medicinal product already authorised, Gemcitabine, Ukrain prolonged the lives of patients by an average of 120 days.

27 The applicant adds that Ukrain has obtained the status of orphan medicinal product for pancreatic cancer in the United States and in Australia, on the basis of the same documents as those supplied to the Commission, and that the inventor of Ukrain was nominated for a Nobel Prize in 2005 and for an Alternative Nobel Prize in 2007.

28 Lastly, the applicant observes that there have been no clinical investigations directly comparing Ukrain with other medicinal products used in the treatment of pancreatic cancer. However, it points to indirect comparisons that have been made between the combination of Gemcitabine with Ukrain and Gemcitabine with Erlotinib. It states that the survival rate is significantly higher in the first case and that the four clinical studies have demonstrated a much higher survival rate where Ukrain is administered alone or in combination with Gemcitabine than where Gemcitabine is administered by itself. It concludes from this that these provisional data have established the greater clinical effectiveness of Ukrain.

29 In the second place, the applicant complains that the Commission's requirements with regard to establishing significant benefit were excessive. It maintains that the conditions imposed by the Committee as regards the Phase II clinical studies which it submitted in reality corresponded to the level of requirement normally imposed for Phase III clinical studies, which are used in the Community authorisation procedure for marketing an orphan medicinal product. In other words, the Committee treated the 'pilot' studies conducted on Ukrain as if they were Phase III studies. The applicant states in that regard that the questions put to Professors N. and K., the experts appointed in the appeal procedure, should have been asked only in the context of the Community marketing authorisation procedure.

30 In the third place, the applicant complains that the principle of equal treatment was infringed. It considers that the Committee imposed on it requirements that were stricter in terms of the criteria to be met and the studies and documentation to be produced in order to obtain designation of Ukrain as an orphan medicinal product than those imposed on sponsors of other medical treatments, such as chimeric antibody to mesothelin and Nimuzuteb. According to the applicant, the sponsors of those products obtained 'orphan medicinal product authorisation' without such extensive studies being required as those which the Commission required for Ukrain.

31 In that regard, the applicant maintains that the Commission took into account inappropriate evidence. It considers that the contested decision was based more on 'market policy' than on a choice made on the basis of established criteria. It therefore complains that the Commission failed to comply with the main objective of Regulation No 141/2000, which is to promote the development of treatments for rare conditions.

32 The Commission disputes the applicant's arguments and contends that this plea should be rejected.

— Findings of the Court

33 First, it should be noted that the procedure relating to orphan medicinal products divides into two separate phases. The first phase covers the designation of the product as an orphan medicinal product; the second covers marketing authorisation for the product that has been designated as an orphan medicinal product and the market exclusivity attaching to it.

34 With regard to the procedure for designation as an orphan medicinal product, Article 3 of Regulation No 141/2000 sets out the criteria which a product must meet in order to be so designated. The sponsor of the orphan medicinal product must in particular establish that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question by the product for which an application for designation as an orphan medicinal product has been made that has been authorised in the Community. If such a method exists, the legislature has made provision for the designation as an orphan medicinal product of any potential medicinal product for the treatment of the same condition provided its sponsor can establish that the medicinal product will be of significant benefit to patients affected by that condition.

35 With regard to significant benefit, it should be noted that this is defined in Regulation No 847/2000 as 'a clinically relevant advantage or a major contribution to patient care'.

36 As for the second phase of the procedure, namely that of marketing authorisation for an orphan medicinal product, that phase does not start until after the product concerned has been designated as an orphan medicinal product.

37 In the present case, the contested decision was taken during the first phase of the procedure, namely that of designation of Ukrain as an orphan medicinal product. It is also agreed between the parties that medicinal products for the treatment of pancreatic cancer had already been authorised on the market and that it was therefore for the applicant to establish that its product would be of significant benefit to patients affected by that disease.

38 On this point, it must be stated that the significant benefit relied upon by the applicant is due to the fact that Ukrain acts only against cancer cells and is therefore not toxic for healthy cells, it prolongs the lives of persons affected by pancreatic cancer and it offers a last resort for patients who can no longer tolerate the toxic effects of other medicinal products.

39 It is in the light of these observations that the complaints contained in the plea alleging infringement of Article 3(1) of Regulation No 141/2000 must be examined.

40 In the first complaint, the applicant submits, in essence, first, that significant benefit does not need to be established by means of a comparison between the medicinal product for which designation as an orphan medicinal product is sought and existing methods of treatment, but must be established in relation to the intrinsic qualities of that product. Secondly, it states that Ukrain does in fact possess intrinsic qualities and thus offers significant benefit.

41 It is clear unequivocally from Article 3(1) of Regulation No 141/2000 and from the definition of 'significant benefit' given in Article 3(2) of Regulation No 847/2000 that

such benefit does not need to be established except in the specific case where a satisfactory method of diagnosis, prevention or treatment of the condition in question has already been authorised.

42 Under the first subparagraph of Article 3(1)(a) and (b) of Regulation No 141/2000, the sponsor of a medicinal product for which designation as an orphan medicinal product is sought is required to establish that the product concerned is intended for the diagnosis, prevention or treatment of a rare condition and that there does not yet exist a satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised. However, the sponsor of a potential medicinal product intended to treat a rare condition for which such a satisfactory method of diagnosis, prevention or treatment already exists must not only establish, under the first subparagraph of Article 3(1)(a), that the medicinal product in question is actually intended for the diagnosis, prevention or treatment of the rare condition, but also, under Article 3(1)(b), that the potential medicinal product will be of significant benefit to patients affected by that condition.

43 Establishing significant benefit therefore takes place in the context of a comparison with an existing authorised medicinal product or method. The 'clinically relevant advantage' and the 'major contribution to patient care', which enable the potential orphan medicinal product to be described as being of significant benefit, can be established only by comparison with treatments that have already been authorised.

44 That interpretation is confirmed by the Communication from the Commission on Regulation (EC) No 141/2000 (see paragraph 5 above), which states that '[t]he applicant is required to establish significant benefit compared with an existing authorised medicinal product or method at the time of designation'.

45 It is apparent from the contested decision and, in particular, from the Committee's opinion annexed to that decision, which forms an integral part of it, that the designation of 'Ukrain' as an orphan medicinal product was refused on the grounds that the significant benefit of Ukrain compared with methods of treatment for pancreatic cancer currently authorised had not been established. The Commission's examination was therefore, rightly, carried out from the viewpoint of comparing Ukrain with existing medicinal products, and it concluded that Ukrain had no significant benefit when compared with the latter.

46 Since, as was stated above, establishing significant benefit takes place in the context of a comparison with an existing authorised medicinal product or method, the Commission did not infringe Article 3(1)(b) of Regulation No 141/2000 in considering that it was for the applicant to establish that Ukrain offered significant benefit compared with medicinal products already authorised in the European Union and that therefore evidence of such advantage could not be supplied by setting out merely the intrinsic qualities of Ukrain without comparing them with those of authorised methods.

47 Hence, the applicant is wrong in submitting that the Commission should have limited its examination of Ukrain to the matter of whether it offered in itself a clinically relevant advantage or a major contribution to patient care, without making a comparison with existing authorised methods of treatment. It is also fruitless for the applicant to argue that, merely by making its assessment of significant benefit in the context of a comparison between Ukrain and medicinal products already authorised, the Commission applied the criterion of clinical superiority provided for in Article 8(3) of Regulation No 141/2000.

48 In a second complaintthe applicant maintains that the Commission's requirements with regard to establishing significant benefit were excessive, since they were requirements normally imposed under Article 8(3) of Regulation No 141/2000 in order to establish the clinical superiority of the medicinal product in question. It considers in

particular that the conditions imposed by the Commission as regards the Phase II clinical studies which it supplied corresponded to the level of requirement normally demanded for Phase III clinical studies, which are used in the Community authorisation procedure for marketing an orphan medicinal product. The applicant states in that regard that the questions put to Professors N. and K., the experts appointed in the context of the appeal procedure, should only have been put in the context of a Community marketing authorisation procedure.

49 That complaint cannot be accepted. It must be recalled, as is stated in the Communication from the Commission on Regulation (EC) No 141/2000 (see paragraph 5 above), that, as there may be little or no clinical experience with the potential medicinal product for which designation as an orphan medicinal product is sought, the justification for significant benefit is likely to be made on assumptions of benefit by the sponsor, which must be supported by available data and/or evidence supplied by the latter.

50 An application for designation may thus, depending on the circumstances, be supported by provisional data resulting from preclinical studies, that is to say, studies conducted on cells and/or animals and not on humans, or, where such exist, on data resulting from clinical studies, that is to say, studies conducted on humans. Although the preclinical studies may, by way of an assumption, provide useful information on the significant benefit a potential medicinal product is likely to offer compared with other authorised substances, clinical studies are even better placed to do so. Such studies are conducted *in vivo* and therefore provide the best possible source of information. If clinical studies find the medicinal product in question is of no significant benefit, such findings will not a priori be called into question by preclinical studies conducted *in vitro*. However, it is possible to envisage a situation in which doubt may be cast on the plausibility of clinical studies because of methodological issues affecting them. Such studies do not necessarily call into question the qualities of the medicinal product. It is therefore easy to envisage in such a situation that reference

would be made to preclinical studies in order to assess the possible existence of significant benefit of the medicinal product in question.

51 In the present case, the applicant based the application for designation of Ukrain as an orphan medicinal product on four clinical studies and on other evidence such as preclinical studies.

52 First, with regard to the clinical studies, the contested decision indicated a number of methodological issues that prevented those studies from being given sufficient scientific credit. Because of those methodological issues, the Committee requested the applicant to supply it with the full original study protocols in order to dispel any doubt regarding the studies. The applicant was unable to provide those documents and the EMA was unable to obtain them despite making requests to that effect to the studies' authors. It is therefore on the basis of the available documents supplied to the Committee that the latter drafted its opinion.

53 In that regard, it is necessary to reject the applicant's argument that the Commission imposed in respect of the Phase II clinical studies the conditions normally required for those in Phase III. The Commission pointed out that two allegedly randomised studies raised a number of issues as regards their equilibrium; that the absence of a full protocol and of all the results prevented an objective evaluation being made of the latter; that the other two studies also presented a number of methodological issues; that the average survival period given in the four reports ranged from 8.1 to 33.8 months; and that such differences might be attributable to the methodological errors mentioned rather than to the effect of treatment with Ukrain. In raising these points, the Commission merely demonstrated the lack of clarity in the methods used in the studies conducted during Phase II. The applicant has therefore by no means shown that the conditions imposed by the Committee in respect of the

Phase II clinical studies supplied by the applicant actually corresponded to the level of requirement normally demanded in respect of Phase III clinical studies.

54 Secondly, since the Commission considered that, because of the doubts surrounding their scientific plausibility, the four clinical studies supplied by the applicant did not establish that Ukrain is of significant benefit to patients affected by pancreatic cancer, it is appropriate to determine whether the Commission should have taken into account other evidence relied upon by the applicant that might establish such benefit.

55 First of all, the applicant refers to a number of preclinical studies from which it is apparent that no other product apart from Ukrain possesses properties that are as beneficial for the treatment of cancer. However, the Commission rightly observed, and this was not seriously challenged by the applicant, that those studies relate to diseases other than pancreatic cancer. As the Commission points out, the applicant does not provide any evidence to show that the results of those studies also apply to pancreatic cancer. Similarly, the applicant has not put forward any argument that would call into question the validity of the reasoning contained in the contested decision that since no comparison was made with existing methods of treatment the preclinical studies were not sufficient to establish that Ukrain would be of significant benefit.

56 Also, it must be held that the applicant has not established that the Commission's considerations concerning the cytotoxicity of Ukrain are manifestly erroneous. First, it is apparent from the contested decision (see pages 40 and 41 of the annex) that the Commission bases its finding on a scientific study (Panzer, 2000), which casts doubt on the selective cytotoxicity of Ukrain. Secondly, the fact that the applicant submits that that study conflicts with other scientific studies, including Panzer (1998), far from undermining the validity of the Commission's reasoning, tends rather to demonstrate the existence of scientific uncertainty on this point. Hence, the Commission cannot be criticised for taking that scientific uncertainty into account. Moreover, acceptance of the applicant's line of argument would mean that the Court would have to undertake a comparison of the merits, from the scientific viewpoint, of each of the

studies put forward by the parties, which would go beyond the limits of its review in this matter.

57 Moreover, the fact that Ukrain has obtained the status of an orphan medicinal product in the United States and in Australia cannot call into question the Commission's finding that it offers no significant benefit. Only the European Union provisions laying down criteria for the designation of orphan medicinal products are relevant, so the fact that Ukrain meets the criteria for designation as an orphan medicinal product in other countries is irrelevant in that regard.

58 Lastly, the applicant cannot rely on the fact that the inventor of Ukrain was nominated for the Nobel Prize in 2005 and for the Alternative Nobel Prize in 2007 in order to challenge the soundness of the contested decision. The Commission did not by any means question the scientific standing of the inventor of Ukrain, but rather it identified a number of scientific methodological issues which cast doubt on the plausibility of the medical findings contained in the clinical studies.

59 A third complaint, alleging infringement of the principle of equal treatment was raised by the applicant. The latter criticises the Commission for using, in order to evaluate Ukrain, different assessment criteria from those to be met by sponsors of other medication-based treatments such as Nimuzuteb and chimeric antibody to mesothelin, and maintains that the requirements imposed on those sponsors, in order to obtain designation as an orphan medicinal product, were not so strict.

60 Also, the applicant claims discrimination on the ground that the Commission took into account inappropriate evidence which was not required in the context of the

procedures for the designation of other pharmaceutical treatments as orphan medicinal products. It maintains that the contested decision was based more on 'market policy' than on a choice made on the basis of established criteria. The Commission submits that that argument was raised for the first time in the reply and is inadmissible according to Article 48(2) of the Court's Rules of Procedure.

61 The Court holds that the complaint alleging infringement of the principle of equal treatment must be rejected. First, the criteria to which the Commission referred are correct, as was explained above. Secondly, even if incorrect criteria had been applied in the procedure for the designation of other medicinal products as orphan medicinal products, the applicant could not validly rely on that circumstance since respect for the principle of equal treatment must be reconciled with the principle of legality, according to which a person may not rely, in support of his claim, on an unlawful act committed in favour of a third party (see, to that effect, Case T-327/94 *SCA Holding* v *Commission* [1998] ECR II-1373, paragraph 160; Case T-106/00 *Streamserve* v *OHIM (STREAMSERVE)* [2002] ECR II-723, paragraph 67; and Case T-23/99 *LR AF 1998* v *Commission* [2002] ECR II-1705, paragraph 367).

62 Moreover, the argument alleging that the Commission took into account inappropriate evidence which was not required in the context of other procedures for designation as orphan medicinal products must be rejected without there being any need to examine its admissibility.

63 The applicant completely fails to show what criterion the Commission applied apart from that of significant benefit, and does not submit any evidence to prove that the Commission has a policy of favouring certain pharmaceutical companies to the detriment of others. On the contrary, it is clear from the contested decision that the Commission did nothing more than seek evidence, as required by Article 3(1) of Regulation

No 141/2000, that Ukrain would be of significant benefit. Thus, the requirement of significant benefit is not the result of 'market policy' but is more a criterion contained in the relevant legislation.

64 In the light of all the foregoing considerations, the plea alleging infringement of Article 3(1) of Regulation No 141/2000 must be rejected.

The second plea: lack of qualification and lack of impartiality on the part of Professor H. W.

— Arguments of the parties

65 In the first place, the appellant submits that Professor H. W., whom the Committee appointed as an expert in the procedure for the designation of Ukrain as an orphan medicinal product, was not qualified to give an opinion on that product since he is not an expert in oncology.

66 In the second place, the applicant argues that Professor H. W. had already given an unfavourable opinion on Ukrain in two procedures relating to Ukrain in Austria, and that that calls into question his scientific impartiality as regards that medicinal product.

67 The applicant puts forward a number of arguments to demonstrate Professor H. W.'s lack of impartiality. First, it submits that he disregarded new results of analyses contained in recent studies.

68 Secondly, it observes that Professor H. W. did not take into consideration, nor did he bring to the attention of the Commission, the fact that treatment with Ukrain facilitates an operation to remove a cancerous tumour, that some of the publications on which he relies are contradictory as regards the alleged toxicity of Ukrain, and that Ukrain is the only treatment for pancreatic cancer that can be administered intramuscularly without causing tissue necrosis.

69 Thirdly, the applicant states that it submitted Phase II studies, that is to say, 'pilot' studies to determine whether the efficacy of Ukrain on very resistant cells of pancreatic cancer *in vitro* could also be established clinically. It criticises Professors H. W., N. and K. for treating those 'pilot' studies as Phase III studies, which normally take place only after an application has been submitted for authorisation to place on the market a medicinal product designated as an orphan.

70 The applicant points out that clinical studies are not an essential precondition for the designation of a medicinal product as an orphan medicinal product. In its view, the Committee almost exclusively used such studies, and the criticisms it considered it could make of them, as its basis in order to justify an unfavourable opinion.

71 The applicant also observes that Professor H. W.'s criticisms of the four clinical studies it submitted correspond almost word for word to those made in the earlier expert

report prepared for the Austrian Ministry of Health. According to the applicant, the irrelevance of those criticisms is illustrated in particular by two questionable comments made against the Gansauge study (2002).

72 The applicant is also of the opinion that the Commission's assertion that Professor H. W.'s vote 'was not taken into account in the decision' is irrelevant. It maintains that the documents used were selected by Professor H. W. and that neither the experts consulted during the appeal procedure nor the Commission accepted any other assessment of Ukrain apart from the one made by Professor H. W.

73 The Commission disputes the applicant's arguments and submits that that plea is unfounded.

— Findings of the Court

74 At the outset, it must be borne in mind that Article 4(3) of Regulation No 141/2000 provides that the members of the Committee may be accompanied by experts.

75 It must also be borne in mind that, in a complex scientific area such as that of orphan medicinal products, in the majority of cases the Commission endorses the opinions of the Committee unless it has other adequate sources of information in the field in question. It is moreover to that effect that the Community legislature envisaged that a case in which a decision was not in accordance with the Committee's opinion would constitute an exceptional situation. Indeed, Article 5(8) of Regulation No 141/2000 provides that '[w]here, in exceptional circumstances, the draft decision is not in

accordance with the opinion of the Committee, the decision shall be adopted in accordance with the procedure laid down in Article 73 of Regulation … No 2309/93'.

76 It should be pointed out therefore, first, that the Committee cannot properly carry out its task unless it is composed of persons possessing the necessary scientific knowledge in the various fields in question or its members are advised by experts having that knowledge (see, to that effect and by analogy, Case C-269/90 *Technische Universität München* [1991] ECR I-5469, paragraph 22).

77 It should be observed, secondly, that the procedure for designating orphan medicinal products is an administrative procedure involving complex scientific assessments in respect of which the Commission has broad discretion. Hence, it is all the more necessary to observe in this case the guarantees conferred by the Community legal order in administrative procedures, including the duty to examine carefully and impartially all the relevant aspects of the individual case. Such an obligation cannot be validly complied with if the Committee's opinion which the Commission takes as its basis has been given by experts who are partial.

78 It is in the light of those observations that the applicant's complaints must be examined.

79 In the first place, with regard to the complaint alleging that Professor H. W., an expert in pharmacology, is not qualified to give an opinion in the matter, it should be pointed out that the applicant bases this complaint essentially on the fact that the latter is not a specialist in cancerous tumours since he is not an oncologist. The main

thrust of that complaint is that only an oncologist would have been qualified to give a scientifically appropriate opinion on Ukrain and that, by not calling on the services of an oncology specialist, the Commission committed a manifest error of assessment.

80 However, the Court considers that no manifest error of assessment was committed by the Commission, either as regards its choice of an expert in pharmacology in general or as regards the choice of Professor H. W. in particular.

81 On the one hand, the Committee's decision to take advice from a specialist in pharmacology in order to assess whether Ukrain is of significant benefit to patients affected by pancreatic cancer appears legitimate. A pharmacologist studies the mechanisms of interactions between an active substance and the organism in which it evolves, in order to then use those results for therapeutic purposes. A specialist in pharmacology is therefore the appropriate expert to give a scientifically relevant opinion on the effects of a potential medicinal product on the organism.

82 On the other hand, it cannot reasonably be denied that Professor H. W. has considerable expertise in pharmacology. It is common ground that he is on the list of European experts, that he was Director of the Institute of Pharmacology at an Austrian university for a number of years and that from 1997 to 2000 he was a member of the Committee for Proprietary Medicinal Products, now the Committee for Medicinal Products for Human Use, at the EMA.

83 Furthermore, Professor H. W. has already been consulted as an expert in two procedures relating to Ukrain in Austria. It is therefore reasonable to assume that he is particularly knowledgeable about the potential medicinal product in question.

84 Hence, the fact that the Committee chose Professor H. W. would appear justified in view of his standing as an acknowledged specialist in pharmacology and of the knowledge he has already acquired on Ukrain.

85 It follows that the complaint alleging that Professor H. W. was not qualified to give an opinion on Ukrain must be rejected.

86 In the second place, it is necessary to examine the complaint alleging that Professor H. W. was not impartial.

87 First, it should be observed that, according to well-established case-law, whilst the Community institutions have broad discretion, respect for the rights guaranteed by the Community legal order in administrative procedures is of even more fundamental importance. Those guarantees include, in particular, the duty of the competent institution to examine carefully and impartially all the relevant aspects of the individual case (see, to that effect, *Technische Universität München*, paragraph 76 above, paragraph 14; Case C-326/05 P *Industrias Químicas del Vallés* v *Commission* [2007] ECR I-6557, paragraph 77; and Case T-167/94 *Nölle* v *Council and Commission* [1995] ECR II-2589, paragraph 73).

88 It should also be recalled that the requirement of impartiality to which the Community institutions are subject also extends to experts consulted in that regard. In particular, where an expert is requested to give an opinion on the effects of a potential medicinal product, it is necessary for that expert to perform his task impartially (see, to that effect and by analogy, Case T-70/99 *Alpharma* v *Council* [2002] ECR II-3495, paragraphs 172, 183 and 211).

89 In that regard, Article 10(1) of the Committee's Rules of Procedure provides that in respect of specific scientific or technical fields the Committee and its working groups may avail themselves of the services of experts included in the European Experts list. Under Article 11(2) and (3) of those rules, the members of the Committee, members of working groups, and experts must not have any direct interests in the pharmaceutical industry which could affect their impartiality and independence and must declare at the beginning of each meeting any specific interests which could be considered to be prejudicial to their independence with respect to the points of the agenda.

90 It should be noted that Professor H. W. made a solemn declaration that he had no direct or indirect interest in the pharmaceutical industry, and this has not been questioned by the applicant. It must therefore be held that Professor H. W. complied with the declaration requirements contained in Articles 10 and 11 of the Committee's Rules of Procedure and has not faced any conflict of interests likely to call into question his impartiality.

91 Secondly, the applicant is wrong in submitting that the mere fact that Professor H. W. has already prepared expert reports in two procedures relating to Ukrain means that he could not act in the same capacity in the administrative procedure that resulted in the adoption of the contested decision without infringing the obligation of impartiality.

92 The only obligation laid down in the Committee's Rules of Procedure which could have led to Professor H. W.'s impartiality being called into question if he had failed to comply with it is the obligation that there should be no conflict of interests with the pharmaceutical industry. As was stated in paragraph 90 above, there is no question of Professor H. W. having any interest that would conflict with the purpose of his task of preparing an expert report.

93 The obligation of impartiality cannot be construed as meaning that there is a legal impediment to an expert being consulted in a procedure for the designation of a medicinal product as an orphan medicinal product solely because he has already given an opinion on the same product in another, national, procedure carried out in a Member State of the European Union.

94 Thirdly, the applicant's attempt to call into question Professor H. W.'s impartiality by relying on a number of circumstances in that regard is fruitless.

95 First of all, even if, as the applicant maintains, Professor H. W.'s comments did correspond almost word for word to those made in the earlier expert report prepared for the Austrian Ministry of Health, this would not demonstrate that Professor H. W. was partial. It could mean that he considered that that was the only scientifically acceptable finding with regard to Ukrain.

96 Also, contrary to the applicant's submission, Professor H. W. did not, when giving his opinion, disregard the recent studies submitted by the applicant. It is apparent from the annex to the contested decision that Professor H. W. took into account studies such as those of Aschhoff (2003) and Gansauge (2007), which took place after the expert opinions he prepared at the request of the Austrian Ministry of Health in connection with two national administrative procedures concerning Ukrain.

97 It is also necessary to reject the applicant's argument that Professor H. W.'s impartiality might be called into question because he knowingly took into account only publications that were unfavourable to Ukrain. Even if Professor H. W. did give more emphasis to publications that were favourable to Ukrain, he still supplied a large amount of unfavourable evidence which alone provided a sufficient basis on which it was reasonable, with complete scientific objectivity, to give an unfavourable opinion on whether Ukrain was of significant benefit.

98 Moreover, the argument that Professor H. W. and Professors N. and K. treated the Phase II clinical studies as if they were Phase III studies must be rejected. As was stated in paragraph 53 above, the Commission merely demonstrated the lack of clarity in the methods used in the studies conducted during Phase II.

99 Lastly, contrary to what the applicant implies, it should be stated that positive elements in certain studies, such as the phenomenon of 'encapsulation of the tumour', were not withheld but were indeed brought to the Committee's attention, so that the members of the Committee gave an unfavourable opinion in the knowledge of all the applicant's observations and explanations.

100 Hence, the applicant has not demonstrated that the opinion given by Professor H. W. was dictated by anything other than purely scientific considerations.

101 It follows from all the foregoing that the plea alleging lack of qualification and lack of impartiality on the part of Professor H. W. must be rejected.

Third plea: manifest errors of assessment on the part of the Commission

— Arguments of the parties

102 The applicant maintains that the Committee's opinion is incorrect.

103 In the first place, the applicant states that the mechanism of action of Ukrain differs from that of authorised medicinal products and that is sufficient reason for it to be designated as an orphan medicinal product. It considers that the action of Ukrain is selective, since it does not damage normal cells and does not therefore have an adverse effect on patients' quality of life. It maintains that, unlike conventional treatments, Ukrain when administered intramuscularly does not cause tissue necrosis. It also submits that Ukrain prolongs the lives of patients, and states in particular that, when combined with Gemcitabine, Ukrain prolongs the lives of patients by 120 days.

104 The applicant maintains that the positive results obtained by administering Ukrain to patients were set out in the application for designation of that product as an orphan medicinal product and were supported by four clinical studies and by some very promising preclinical studies. As regards the clinical studies, the applicant states that it is apparent from them that indirect comparisons between the combination of Gemcitabine with Ukrain, on the one hand, and of Gemcitabine with Erlotinib, on the other hand, demonstrated the greater efficacy of Ukrain. As for the preclinical studies, the applicant points out that although a difference is often found in pharmacology between successful preclinical results and disappointing clinical results, that was not

the case with Ukrain. It therefore considers that that evidence should have enabled it to obtain the designation of Ukrain as an orphan medicinal product.

105 In that regard, in the second place, the applicant denies the methodological issues alleged by the Committee, and by the experts, Professor H. W. and Professors N. and K., in response to the questions put by the Committee.

106 With regard to the study by Zemskov (2002), the applicant denies that the statistical methods were not specified in it, pointing out that the study in question mentions Kaplan-Meier survival curves and that a log-rank test was applied. As regards Aschhoff (2003), the applicant submits that this clearly states that 28 patients were recruited between August 1997 and December 2003, of whom 21 did not respond to Gemcitabine and 7 rejected chemotherapy, from which it can be inferred that at least 21 of the 28 patients were already at an advanced stage and had exhausted all possible treatment options. It adds that, so far as the two studies mentioned above are concerned, the small number of patients was due to the fact that the two clinics involved in the studies did not specialise in the treatment of pancreatic cancer.

107 With regard to Gansauge (2002), the applicant submits that the criteria used to evaluate the stage of the patients' disease (staging) in that study were internationally recognised by the International Union Against Cancer (UICC) and were therefore clear.

108 With regard to Gansauge (2007), the applicant relied on the fact that that publication contained additional data on the advantage of adjuvant therapy, combining Gemcitabine and Ukrain, and on the resulting substantial increase in the survival rate.

109 In conclusion, the applicant considers that the Committee's expert report was not drafted objectively. In that connection, it observes that some of the scientific publications cited were misinterpreted or even disregarded. It submits that the assertion that 'methodological irregularities' might have influenced the results of the analyses in favour of Ukrain is incorrect and unfounded.

110 The Commission contends that this plea should be rejected.

— Findings of the Court

111 It should be observed first of all that the Commission must be recognised as enjoying a broad discretion in the areas in which it must undertake complex technical and/or scientific assessments. As part of its judicial review, the Community judicature must determine whether the relevant procedural rules have been complied with, whether the facts established by the Commission are correct and whether there has been a manifest error of appraisal of those facts or a misuse of powers (*Industrias Químicas del Vallés* v *Commission*, paragraph 87 above, paragraph 76; Joined Cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00 *Artegodan and Others* v *Commission* [2002] ECR II-4945, paragraph 201; and Case T-326/07 *Cheminova and Others* v *Commission* [2009] ECR II-2685, paragraph 107).

112 Next it should be stated that a feature of the procedure introduced by Article 5 of Regulation No 141/2000 is the essential part assigned to an objective and in-depth scientific assessment by the Committee of the effect of the potential medicinal products considered. Since the Commission is not in a position to carry out scientific assessments of the efficacy and/or harmfulness of a medicinal product during the orphan medicinal product designation procedure, the aim of the mandatory consultation of

the Committee 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, *Artegodan and Others* v *Commission*, paragraph 111 above, paragraph 198). Thus, although the Committee's opinion does not bind the Commission, it is none the less extremely important. In that regard, as was pointed out in paragraph 75 above, it is apparent from Article 5(8) of Regulation No 141/2000 that a case in which a decision is not in accordance with the Committee's opinion was envisaged as constituting an exceptional situation.

113 Lastly, it is apparent from Article 1 of the contested decision that the designation of Ukrain as an orphan medicinal product for the indication 'Treatment of pancreatic cancer' was refused for the reasons stated in the Committee's report annexed to that decision. It must therefore be held that, in this case, the Commission did not depart from the Committee's opinion and on the contrary endorsed the findings of that opinion.

114 The Court therefore considers that review of a manifest error of assessment must be conducted in respect of all the considerations contained in the contested decision, and also those to which it refers, including the annex, which therefore forms an integral part of the contested decision.

115 Review of a manifest error of assessment involves, initially, cataloguing the essential information contained in the contested decision. In the first four sections of the annex to the contested decision, the Commission explains that the applicant took as its basis four clinical studies in order to demonstrate the therapeutic qualities of Ukrain: Zemskov (2002), Gansauge (2002), Aschhoff (2003) and Gansauge (2007). It states, however, that those four studies from which the clinical data concerning

pancreatic cancer were derived contained methodological and practical issues which seriously damaged their usefulness when it came to assessing the medical plausibility of the findings and, in particular, the existence of significant benefit.

116 The Commission explains that those four studies had been conducted using a total of 190 patients affected by pancreatic cancer, and that it was claimed in those studies that there was a substantial effect on the survival rate of those patients who were treated with Ukrain. The Commission notes, however, that two allegedly randomised studies raised a number of issues regarding their equilibrium, which seriously affected the possibility of a clear interpretation of the results, and that the absence of a full protocol and of all the results did not permit an objective assessment to be made of them. The Commission stated in that regard that the EMA had asked the applicant in vain on several occasions to provide it with those studies. It also considered that the two other studies likewise contained a number of methodological issues. It found that the average survival period given in the four reports ranged from 8.1 to 33.8 months. It stated that the applicant had accepted those differences and had attributed them to the 'differences in terms of population and dosage used'. The Commission for its part considered that those differences might be attributable to some of the methodological errors referred to rather than to the effect of the treatment. It also noted that a recent independent analysis (Ernst and Schmidt, 2005) concerning the potential effectiveness of Ukrain in oncology, which was published in a journal and had been subject to peer review, had found that the methodological quality of most studies on Ukrain was poor, that the interpretation of several trials was impeded by other problems, that numerous caveats prevented a positive conclusion, and that rigorous independent studies were urgently needed.

117 The Commission considered that the documentation available did not contain any independent study of that type and stated, in that regard, that when other researchers had tried to study Ukrain in a Phase II clinical trial in order to establish its efficacy

in various forms of cancer they had stated that they had not been able to obtain the medicinal product (Farrugia and Slevin, 2000).

118 Furthermore, the Commission considered that the assertion of a significant benefit as compared with available methods of treatment, in particular as compared with authorised medicinal products, used to treat the same condition (Gemcitabine and Erlotinib), was not sufficiently substantiated by the available evidence, in view of the conflicting preclinical evidence, methodological issues and the lack of reproducibility noted in specialist literature.

119 Because of doubts as to the plausibility of the published data, the Commission stated that it had requested the applicant to provide it with the full original study protocols and study reports in order for it to be able to assess the data supplied, in the context of the justifications for the assertions of significant benefit. It noted that the applicant had not been able to supply those documents and had justified this by the fact that the four clinical studies on which the assertions of significant benefit were based were the property of the researchers who had conducted them. The Commission stated that the EMA had contacted the four authors of the clinical studies in question, asking them for information concerning the methods and the results. It observed that the information supplied by Dr Gansauge did not contain any new evidence and that no information had been supplied with regard to the Zemskov study.

120 Lastly, the Commission stated that the applicant was correct in stating that submission of those data was not compulsory at the stage of designation as an orphan medicinal product, but that it was difficult to accept the assertion of significant benefit solely on the basis of data published in specialist literature, given the many methodological issues raised in those articles.

121 In the fifth section of the annex to the contested decision, the Commission stated that, in accordance with Article 5(7) of Regulation No 141/2000, the applicant had submitted, on 6 September 2007, detailed grounds for the appeal of 25 June 2007 against the unfavourable opinion which the Committee had given on 31 May 2007. The Commission also noted that, during the appeal procedure, two experts had been appointed, Professors K. and N., whose task was to answer three questions. In the first question, the experts were asked whether they agreed with the Committee's opinion that the available evidence was insufficient to establish that Ukrain was of significant benefit. In the second question, the experts were asked whether they shared the Committee's point of view regarding the existence of methodological issues affecting the four studies relied upon by the applicant. The third question was whether the detailed grounds clarified the issues raised in the context of the first opinion.

122 The annex shows that the experts gave an affirmative reply to the first two questions. As regards the third question, they considered that the applicant had not provided any clarification of the issues raised in the context of the first opinion.

123 The Commission also set out in the annex the exhaustive replies which had been given to the applicant's arguments, and hence the reasons why the existence of significant benefit had not been established.

124 It is in relation to all that evidence contained in the contested decision, and in the annex which forms an integral part of it, that it is necessary, next, to determine whether it is possible to establish from the applicant's arguments that manifest errors of assessment were committed.

125 In the first place, it is appropriate to consider the applicant's argument based on the properties of Ukrain. The applicant contends that, unlike medicinal products already authorised intended for the treatment of pancreatic cancer, Ukrain's action is selective, since it does not cause the destruction of healthy cells and acts only on cancer cells, it has no significant side-effects and it prolongs the life expectancy of patients. Although, in a comparison with the qualities of authorised medicinal products, it cannot be excluded that such properties might be of significant benefit within the meaning of Article 3(1)(b) of Regulation No 141/2000 to persons affected by pancreatic cancer, in the present case it is the scientific methodology per se of the studies on which those findings are based which is called into question.

126 That is why it is necessary to examine whether the applicant's arguments call into question the criticisms made by the experts and the Commission of the various studies relied upon in support of its application.

127 First, the applicant disputes the findings made by Professor K., in the appeal procedure, that the studies by Zemskov (2002) and Aschhoff (2003) involved a small number of patients over a very long time. However, it merely states that the number of patients is small because the two clinics concerned in the studies do not specialise in the treatment of pancreatic cancer. It is not possible to show on the basis of that explanation that any manifest error of assessment was committed in that regard.

128 Secondly, it is necessary to determine whether, as the applicant submits, the studies on which it relies do not contain methodological issues that affect them.

129 First of all, with regard to Zemskov (2002), the applicant denies that the statistical methods were not stated in that study, pointing out that the study in question referred to Kaplan-Meier survival curves and that a log-rank test was applied. Although it is true that those two statistical methods do appear in the Zemskov study, it should be observed that the Commission's criticism regarding the absence of statistical methods relates to a stage before those methods. The Commission rightly considered that in order to be able to evaluate those survival curves of the participants in the study it was necessary to indicate the composition of the groups of participants and the relevant criteria (age, sex, and so forth) of the participants comprising the different groups. The Commission, without being contradicted on this point by the applicant, concluded that that study did not contain any information in that regard.

130 Also, so far as Gansauge (2002) is concerned, it is fruitless for the applicant to submit that the staging criteria used in that study were recognised by the UICC. As was observed with regard to Zemskov (2002), the Commission stated that the methodological issue found in that study occurred at an earlier stage. It explained that the inclusion criteria used in the study were imprecise because the criteria for evaluating the staging of the patients had not been specified before they were included in the study, nor had it been specified whether endoscopy had been carried out on all the patients. The Commission stated that such information could have consequences for the survival of a patient irrespective of the treatment given.

131 The applicant merely observed that those criteria were recognised by the UICC and did not put forward any argument challenging that statement. In those circumstances, it must be held that the Commission did not commit a manifest error of assessment in considering that the findings with regard to Ukrain contained in Gansauge (2002) were open to question and did not establish that Ukrain would be of significant benefit to patients affected by pancreatic cancer.

132 Also, with regard to Aschhoff (2003), the Commission pointed out that it was a retrospective study and that the criteria for inclusion and attribution were not given, so that a 'bias', that is to say, a methodological error which leads to incorrect results, could not be excluded. The applicant's reasoning that it was clear from the study that 28 patients were recruited between August 1997 and December 2003, 21 of whom did not respond to Gemcitabine and 7 of whom had rejected chemotherapy, and that it could be inferred from this that at least 21 of the 28 patients were already at an advanced stage and had already exhausted all treatment options, is not sufficient to challenge the Commission's legitimate reservations with regard to that study.

133 Lastly, with regard to Gansauge (2007), a study concerning adjuvant therapy combining Gemcitabine and Ukrain, it should be noted that the Commission considered that it did not permit the effect of Ukrain to be distinguished from that of Gemcitabine or make it possible to establish whether the treatment was generally effective. The Commission pointed out that there was no 'placebo group', which is normally necessary where there is no medicinal product authorised for the adjuvant therapy, so the comparison had been made using historic data. The Commission stated that all the patients taking part in that study showed healthy resection rates following surgery and therefore constituted a highly preselected group for which prognosis was better. Far from contradicting the Commission's observations, the applicant merely stated that that publication contained additional data on the advantage of the adjuvant therapy combining Gemcitabine and Ukrain and on the resulting substantial prolongation of the length of survival. Such considerations by no means show that the Commission committed a manifest error of assessment.

134 In the second place, the applicant's argument that the mechanism of action of Ukrain is different from that of the authorised substances and that that reason alone is sufficient to establish the existence of significant benefit must be rejected. As was stated in the analysis of the first plea, the significant benefit of Ukrain cannot be established solely on the basis of the mechanisms of action of that medicinal product but requires a comparison of that product with products that have already been authorised. The

mere fact that the mechanism of action of one medicinal product is different from that of another that has already been authorised does not in itself mean that the first product is of significant benefit to those affected by the condition which both products are supposed to combat. If the results of using the first medicinal product are not different from those obtained by using the second, it is of little relevance that both products in essence achieve the same results by different mechanisms of action, and there can be no question in that case of significant benefit resulting from the use of the first product.

135 Similarly, it is fruitless for the applicant to reiterate, in respect of the Committee's observations made at the end of the appeal procedure, its considerations concerning the fact that Ukrain's properties mean that it is of significant benefit. It should be made clear that the experts consulted during the original procedure and the appeal procedure and also the Committee members found serious methodological issues in the four studies on which the applicant relies. It is because of those methodological issues that the Commission considered that it could not assign objective scientific value to the results of those studies. Hence, by merely reiterating the result of those studies, the applicant failed to demonstrate that the Commission committed a manifest error of assessment.

136 In that context, the applicant's criticisms of the considerations regarding the toxicity of the medicinal product contained in the contested decision must also be rejected. The Commission took Panzer (2000) as a basis for its reservations regarding the alleged selective cytotoxicity of Ukrain's constituents. As was stated in paragraph 56 above, in such a complex scientific field this is a matter for the Commission's broad discretion. Also, the mere fact that the findings of that study have not been confirmed by other reports does not in itself demonstrate that a manifest error of assessment was committed by the Commission.

137 For all the above reasons, the plea alleging manifest errors of assessment must be rejected.

138 Since all the claims for annulment put forward by the applicant have failed, the present action must be dismissed.

Costs

139 Under Article 87(2) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. Since the applicant has been unsuccessful, it must be ordered to pay the costs, in accordance with the form of order sought by the Commission.

On those grounds,

THE GENERAL COURT (Fifth Chamber)

hereby:

1. Dismisses the action;

2. Orders Now Pharm AG to pay the costs.

Vilaras Prek Ciucă

Delivered in open court in Luxembourg on 9 September 2010.

[Signatures]

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