Reports of Cases

JUDGMENT OF THE COURT (Eighth Chamber)

4 October 2024*

(Appeal – Regulation (EC) No 141/2000 – Orphan medicinal products – Articles 3 and 8 – Concept of 'significant benefit' – Concept of 'clinical superiority' – Regulation (EC) No 847/2000 – Article 3 – Marketing authorisation for the medicinal product for human use Tobramycin VVB – Period of market exclusivity of Tobi Podhaler, containing the active substance tobramycin – Derogation from that market exclusivity)

In Case C-237/22 P,

APPEAL under Article 56 of the Statute of the Court of Justice of the European Union, brought on 4 April 2022,

Mylan IRE Healthcare Ltd, established in Dublin (Ireland), represented initially by L. Bidaine and I. Vernimme, and subsequently by L. Bidaine, Q. Declève and I. Vernimme, avocats,

appellant,

the other parties to the proceedings being:

European Commission, represented initially by K. Mifsud-Bonnici and A. Sipos, and subsequently by E. Mathieu, K. Mifsud-Bonnici, A. Sipos and A. Spina, acting as Agents,

defendant at first instance,

supported by:

European Medicines Agency (EMA), represented initially by S. Marino, S. Drosos and C. Schultheiss, subsequently by S. Marino and S. Drosos, and finally by S. Drosos, acting as Agents,

intervener in the appeal,

VVB UAB, established in Kaunas (Lithuania), represented by V. Horcajuelo Rivera, E. Rivas Alba and M.C. Yáñez Cañas, abogados, and by M. Martens and B. Mourisse, advocaten,

intervener at first instance,

THE COURT (Eighth Chamber),

* Language of the case: English.

composed of N. Piçarra, President of the Chamber, K. Jürimäe (Rapporteur), President of the Third Chamber, acting as a Judge of the Eighth Chamber, and M. Gavalec, Judge,

Advocate General: N. Emiliou,

Registrar: A. Lamote, Administrator

having regard to the written procedure and further to the hearing on 20 September 2023,

after hearing the Opinion of the Advocate General at the sitting on 11 July 2024,

gives the following

Judgment

1 By its appeal, Mylan IRE Healthcare Ltd ('Mylan') asks the Court of Justice to set aside the judgment of the General Court of the European Union of 26 January 2022, *Mylan IRE Healthcare* v *Commission* (T-303/16, 'the judgment under appeal', EU:T:2022:25), by which the General Court rejected the application – initially brought by Novartis Europharm Ltd, for which Mylan substituted itself as the applicant – for annulment of Commission Implementing Decision C(2016) 2083 final of 4 April 2016 concerning, in the framework of Article 29 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations for 'Tobramycin VVB and associated names', medicinal products for human use which contain the active substance 'tobramycin' ('the decision at issue').

Legal context

Regulation No 141/2000

2 Under Article 1 of 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), as amended by Regulation (EC) No 596/2009 of the European Parliament and of the Council of 18 June 2009 (OJ 2009 L 188, p. 14) ('Regulation No 141/2000'):

'The purpose of this Regulation is to lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products.'

3 Article 3 of that regulation, entitled 'Criteria for designation', provides:

'1. 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 [European] 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.

2. The [European] Commission shall, in accordance with the regulatory procedure referred to in Article 10a(2), adopt the necessary provisions for implementing paragraph 1 of this Article in the form of an implementing Regulation.'

4 Article 8 of that regulation, entitled 'Market exclusivity', provides, in paragraphs 1 and 3 thereof:

'1. Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to [Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization 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)] or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of [Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products (OJ, English Special Edition, Series I Volume 1965-1966 p. 20.)] or Article 9(4) of [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)], and without prejudice to intellectual property law or any other provision of Community law, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

…

3. By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

(a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.'

Regulation (EC) No 847/2000

5 In accordance with Article 3(2) of Regulation No 141/2000, the Commission adopted 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).

6 Article 3(2) and (3)(d) of Regulation No 847/2000 provides:

'2. 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.

…

'3. For the purposes of the implementation of Article 8 of Regulation (EC) No 141/2000 on orphan medicinal products, the following definitions shall apply:

…

(b) "clinically superior" means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways:
(1) greater efficacy than an authorised orphan medicinal product (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials are generally necessary, however comparisons based on other endpoints, including surrogate endpoints may be used. In any case, the methodological approach should be justified;

or
(2) greater safety in a substantial portion of the target population(s). In some cases direct comparative clinical trials will be necessary;

or
(3) in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.'

Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products

7 Under Part B, Point 5 of the Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (OJ 2016 C 424, p. 3):

'… "significant benefit" is established by means of comparison with existing authorised medicinal products or methods, not just by assessing the intrinsic qualities of the product in question.

…

– "a clinically relevant advantage" may be based on:

– improved efficacy for the entire population suffering from the condition or a particular population subset or a subset that is resistant to the existing treatments; or

– a better safety profile or a better tolerability for the entire population suffering from the condition or for a particular subset.

…'

The background to the dispute and the decision at issue

8 The background to the dispute is set out in paragraphs 1 to 18 of the judgment under appeal and may, for the purposes of this appeal, be summarised as follows.

9 In 1999, Novartis Pharmaceuticals UK obtained a marketing authorisation for Tobi, a medicinal product containing the active substance tobramycin for inhalation by nebuliser, indicated for the treatment of pulmonary infection due to the bacterium *Pseudomonas aeruginosa* in cystic fibrosis patients.

10 On 17 April 2003, Chiron Corporation Ltd was granted the designation as an 'orphan medicinal product', pursuant to Regulation No 141/2000, in the version applicable on that date, for the medicinal product Tobramycin (inhalation powder), intended, like Tobi, for the treatment of the abovementioned pulmonary infection in cystic fibrosis patients. In order to obtain that designation, Chiron Corporation had to establish that Tobramycin (inhalation powder) was of significant benefit to the relevant patients compared with existing therapies, including Tobi. In order to demonstrate that there was a significant benefit, Chiron Corporation relied on the major contribution of Tobramycin (inhalation powder) to those patients' care owing to the fact that it significantly reduced delivery time of the medicinal product by comparison with Tobi and it could be administered with a portable delivery system, which was an added convenience for those patients and was potentially an improvement in compliance with the treatment regime.

11 In 2006, the designation as an orphan medicinal product of Tobramycin (inhalation powder) was transferred to Novartis Europharm, after its acquisition of Chiron Corporation.

12 On 20 July 2011, on the basis of that designation, the Commission adopted Implementing Decision C(2011) 5394 final granting marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for 'Tobi Podhaler – Tobramycin', an orphan medicinal product for human use. By that decision, Novartis Europharm obtained the marketing authorisation for the medicinal product Tobi Podhaler.

13 As an orphan medicinal product, Tobi Podhaler enjoyed, from when its marketing authorisation was granted, a 10-year period of market exclusivity, in accordance with Article 8(1) of Regulation No 141/2000. That market exclusivity allowed the holder of the marketing authorisation to prevent the market entry of similar competing medicinal products, subject to certain derogations. The period of market exclusivity granted to Tobi Podhaler expired on 25 July 2023.

14 On 2 May 2014, VVB UAB submitted a marketing authorisation application for the medicinal product Tobramycin VVB and associated names ('Tobramycin VVB'). Since Tobramycin VVB was similar to Tobi Podhaler, as an orphan medicinal product for the same therapeutic indication, within the meaning of Article 3(3)(b) of Regulation No 847/2000, VVB applied for a derogation from the market exclusivity which Tobi Podhaler enjoyed, in accordance with Article 8(3)(c) of Regulation No 141/2000. In that regard, it claimed that Tobramycin VVB was clinically superior to Tobi Podhaler, given its greater safety in a substantial portion of the target population.

15 On 28 January 2016, in the context of an assessment of the dossier, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a scientific opinion in which it considered that, in the context of Article 8(3)(c) of Regulation No 141/2000, read in conjunction with Article 3(3)(d)(2) of Regulation No 847/2000, the clinical superiority of Tobramycin VVB over Tobi Podhaler in a substantial portion of the target population could be established, with the result that the marketing authorisation could be granted for Tobramycin VVB. The scientific opinion was adopted by consensus and was sent to the Commission.

16 On 4 April 2016, the Commission adopted the decision at issue. By that decision, the Commission found, on the basis of that scientific opinion, that Tobramycin VVB fulfilled the criteria provided for in Article 8(3) of Regulation No 141/2000.

The procedure before the General Court and the judgment under appeal

17 By application lodged at the Registry of the General Court on 14 June 2016, Novartis Europharm brought an action for annulment of the decision at issue.

18 By document lodged at the Court Registry on 28 September 2016, VVB applied for leave to intervene in the proceedings in support of the form of order sought by the Commission. By order of 10 March 2020, the President of the Ninth Chamber of the General Court granted VVB leave to intervene.

19 Following an agreement to transfer the marketing authorisation for Tobi Podhaler from Novartis Europharm to Mylan, the Commission adopted two decisions transferring rights, by which Mylan became, as from 1 July 2019, the holder of the designation as an orphan medicinal product of Tobi Podhaler and of its marketing authorisation and, therefore, of the market exclusivity granted to that medicinal product.

20 By order of 18 December 2019, *Novartis Europharm* v *Commission* (T-303/16, EU:T:2019:908), the General Court authorised Mylan to substitute itself for Novartis Europharm as applicant in that case and reserved the costs.

21 In support of its action before the General Court, Mylan raised two pleas in law, alleging, first, infringement of Article 8(1) and (3) of Regulation No 141/2000 and, second, breach of the duty of care.

22 The first plea consisted, in essence, of three complaints. The first complaint alleged that the data from the study on which the CHMP relied were insufficient to reach a finding that Tobramycin VVB was clinically superior to Tobi Podhaler. The second complaint alleged errors in the assessment of that clinical superiority. The third complaint alleged failure to observe the objective and system of Regulation No 141/2000.

23 The General Court rejected all those complaints as unfounded.

24 As regards, specifically, the second complaint, the General Court first noted that the designation of a medicinal product as an orphan medicinal product was provided for in two situations referred to in Article 3(1)(b) of Regulation No 141/2000. In paragraph 93 of the judgment under appeal, it noted that, according to the second situation, the sponsor of the medicinal product which is the subject of the application for such a designation had to demonstrate that the medicinal product would be of significant benefit. It is also stated in paragraphs 94 and 95 of that judgment, first, that the concept of 'significant benefit' of a medicinal product was defined in Article 3(2) of Regulation No 847/2000 as 'a clinically relevant advantage or a major contribution to patient care' and, second, that the establishment of such a benefit in the context of the second situation mentioned above had to be by comparison with treatments that had already been authorised, according to strict criteria.

25 In paragraphs 97 to 102 of the judgment under appeal, the General Court, in addition, noted that once the designation as an orphan medicinal product had been obtained, the sponsor could apply for a marketing authorisation. Once the marketing authorisation has been issued, the competent authorities, under Article 8(1) of Regulation No 141/2000, must not, for a period of 10 years, accept another application for a marketing authorisation in respect of a similar medicinal product for the same therapeutic indication or indications included in the designation of that product as an orphan medicinal product. It nevertheless noted that Article 8(3) of that regulation provided for three situations in which it was possible to derogate from the abovementioned 10-year exclusivity period and that the third of those situations provided for such a derogation where an application for a marketing authorisation was submitted for a medicinal product similar to an orphan medicinal product already authorised which was more effective or otherwise clinically superior.

26 The General Court then noted, in paragraphs 103 and 104 of the judgment under appeal, that the scope and extent of judicial review was, where the Commission must undertake complex technical or scientific assessments, confined to determining whether the relevant procedural rules had been complied with, whether the facts established by the Commission were correct and whether there had been a manifest error of appraisal of those facts or a misuse of powers.

27 Lastly, in paragraphs 105 to 109 of the judgment under appeal, the General Court stated that the Commission relied, in the context of the procedure introduced by Article 5 of Regulation No 141/2000, on a scientific assessment of the effect of the medicinal product in question, carried out by a scientific committee. It noted (i) that, in the present case, the Commission had authorised the marketing of Tobramycin VVB for the reasons set out in the CHMP report referred to in paragraph 15 above which concluded that that product was clinically superior to

Tobi Podhaler and (ii) that, following that scientific opinion, it had also authorised the marketing of Tobramycin VVB on the ground that it was safer in a substantial portion of the target population.

28 It is in the light of those considerations that the General Court examined the arguments put forward by Mylan in the second complaint of the first plea, which concerned, in essence, the alleged inconsistencies and contradictions following from misinterpretations of the concept of 'significant benefit', referred to in Article 3(2) of Regulation No 141/200, and of the concept of 'clinical superiority', referred to in Article 8(3) of that regulation.

29 In that regard, in paragraphs 113 and 114 of the judgment under appeal, the General Court noted that, while the concept of 'significant benefit' constituted a condition for obtaining the designation of orphan medicinal product, that of 'clinical superiority', for the purposes of Article 8(3)(c) of that regulation, was one of the conditions under which a derogation from the market exclusivity of an orphan medicinal product could be granted to a similar medicinal product. It considered that the latter concept covered, as alternatives, greater efficacy, greater safety in a substantial portion of the target population or a major contribution to diagnosis or to patient care.

30 Based on those definitions, the General Court examined, in paragraphs 115 to 121 of the judgment under appeal, whether the assessment criteria for those two concepts were the same, as Mylan claimed. While observing, first of all, that those concepts had different purposes and scope, it concluded that the concepts of 'significant benefit' and 'clinical superiority' were based on the same criteria, namely greater efficiency, greater safety or a major contribution to patient care. The General Court also specified that those criteria were not cumulative.

31 As regards, in particular, the demonstration of significant benefit on the basis of the criterion of major contribution to patient care, examined in paragraphs 122 to 124 of the judgment under appeal, the General Court noted that the sponsor also had to prove that the medicinal product for which he intended to seek designation as an orphan medicinal product was at least equivalent to, or not inferior to, the medicinal products already authorised in terms of efficacy and safety. With this in mind, the General Court deduced that the criteria for assessing significant benefit were identical to those for assessing clinical superiority and that they were not cumulative. It added that they '[had to] be assessed as a whole on the basis of a weighting and overall evaluation of the benefit/risk balance'.

32 The General Court pointed out, in paragraph 125 of the judgment under appeal, that, in the case at hand, the Committee for Orphan Medicinal Products (COMP) had followed such a logic in order to conclude, in its opinion on Tobi Podhaler, that that medicinal product was of significant benefit to persons affected by the orphan disease in question, justified by a major contribution to patient care owing to a reduction in the administration time of the active substance and a more convenient form of administration by comparison with Tobi.

33 As regards the assessment of the clinical superiority of Tobramycin VVB over Tobi Podhaler, examined in paragraphs 126 to 129 of the judgment under appeal, the General Court noted that the study which had been used to assess the significant benefit of Tobramycin VVB as compared with Tobi Podhaler had been considered sufficient to support the finding that Tobramycin VVB was clinically superior to Tobi Podhaler, in so far as Tobramycin VVB was identical to Tobi. According to the General Court, that led the Commission, by the decision at issue, to authorise the marketing of Tobramycin VVB on the basis of the clinical superiority of the latter, based on the criterion of greater safety in a substantial portion of the target population.

34 The General Court considered, in paragraphs 131 to 133 of the judgment under appeal, that the Commission had correctly found Tobramycin VVB to be clinically superior to Tobi Podhaler in so far as, first, like the criteria for assessing significant benefit, the assessment criteria for clinical superiority were not cumulative. Second, the criterion of greater safety, for the assessment of clinical superiority, had to be assessed individually, without establishing an overall benefit/risk balance for the population as a whole 'as is the case for significant benefit'. The General Court thus rejected Mylan's argument that, where clinical superiority of a medicinal product is based on its greater safety, it must be demonstrated for the whole of the target population or, at least, for a substantial portion of that population, in such a way that the benefit/risk balance is improved.

35 The General Court then examined Mylan's argument that it is 'inconsistent and illogical' to conclude that Tobi Podhaler provides a significant benefit in comparison with Tobi or Tobramycin VVB according to one of the criteria and, at the same time and on the basis of the same data, that Tobi or Tobramycin VVB is clinically superior to Tobi Podhaler according to another criterion, since the comparability of the efficiency and safety profiles of the two medicinal products at issue was a condition justifying the significant benefit of Tobi Podhaler.

36 In paragraphs 135 to 137 of the judgment under appeal, the General Court noted that the Commission had itself, during the procedure for granting the marketing authorisation to Tobramycin VVB, submitted that alleged inconsistency to EMA, which had replied that the conclusions of COMP and the CHMP were well founded. The General Court emphasised that, even if the efficiency and safety profiles of Tobi and Tobi Podhaler had been found to be comparable or similar for the target population taken as a whole, that did not mean that they were equivalent for all subsets of that population. In particular, according to the General Court, it is apparent from the studies annexed to the decision at issue that Tobi Podhaler posed a higher risk of incidence of cough than Tobi or Tobramycin VVB, with the result that the rate of discontinuation of treatment with Tobi Podhaler was higher than that of treatment with Tobi and Tobramycin VVB, in particular in adults.

37 First of all, in paragraph 138 of the judgment under appeal, the General Court deduced from this that the Commission could not be criticised for having concluded that a portion of the target population could not use Tobi Podhaler due to the development of intolerance, which is borne out by the summary of that medicinal product's characteristics. It pointed out that that summary contained a special warning concerning the cough risk and recommended the use of Tobi in the event of intolerance. It considered that, since Tobramycin VVB was a generic copy of Tobi, that medicinal product could present a new alternative solution to Tobi Podhaler, in particular in Estonia, Latvia and Lithuania, where Tobi is not authorised.

38 Next, the General Court held, in paragraph 139 of the judgment under appeal, that the Commission did not make a manifest error of assessment in concluding that a cough was described as a 'very common adverse event' in that it occurred in more than 10% of cases, which constituted a substantial portion of the target population. It considered that the 3.9% rate of discontinuing treatment with Tobi Podhaler because of a cough was irrelevant, because other patients developing a cough from taking that medicinal product could also develop intolerance justifying the use of an alternative medicinal product.

39 Lastly, the General Court held, in paragraph 140 of the judgment under appeal, that the Commission had rightly considered that the inhalation duration was not a relevant criterion for the assessment of the clinical superiority of Tobramycin VVB because that duration had no impact on patients who may develop an intolerance to Tobi Podhaler.

40 As regards the second plea, the general Court held that the Commission had not infringed the duty of care or the principle of impartiality by not asking the CHMP for the reasons for the alleged lack of impact of the available clinical data and for not taking them all into account.

41 The General Court therefore dismissed the action in its entirety.

Procedure before the Court and forms of order sought by the parties to the appeal

42 By its appeal, Mylan claims that the Court should:

– set aside the judgment under appeal;

– if the Court considers that the state of the proceedings so permits, annul the decision at issue, otherwise, refer the case back to the General Court;

– order the Commission to pay the costs that it incurred as a result of both the appeal proceedings and the proceedings at first instance, and

– order VVB to bear its own costs incurred as a result of those two sets of proceedings.

43 The Commission contends that the Court should:

– dismiss the appeal; and

– order Mylan to pay the costs.

44 VVB contends that the Court should:

– dismiss the appeal; and

– order Mylan to pay the costs that VVB incurred as a result of both the appeal proceedings and the proceedings at first instance.

45 By order of the President of the Court of 22 September 2022, EMA was granted leave to intervene in support of the form of order sought by the Commission.

The appeal

46 In support of its appeal, Mylan raises two grounds of appeal, the first alleging an error of law in the interpretation of the concept of ‘clinical superiority’, for the purposes of Article 8(3)(c) of Regulation No 141/2000, and the second alleging insufficient reasoning of its conclusion that Tobi and Tobramycin VVB were safer than Tobi Podhaler in a substantial portion of the target population.

The first ground of appeal

Arguments of the parties

47 Mylan claims that the General Court made an error of law in the interpretation of the concept of 'clinical superiority', for the purposes of Article 8(3)(c) of Regulation No 141/2000. First, the General Court found, in paragraphs 120 and 124 of the judgment under appeal, that the concepts of 'significant benefit' and 'clinical superiority' were based on the same criteria, that those criteria were not cumulative and that they had to be assessed on the basis of a weighting and 'overall evaluation of the benefit/risk balance'. Second, the General Court held, in paragraph 132 of the judgment under appeal, with regard to the concept of 'clinical superiority', that the criterion of 'greater safety in a substantial portion of the target population(s)' had to be assessed individually, without establishing an overall risk/benefit balance for the population as a whole, as is the case for significant benefit.

48 According to Mylan, there is no reason justifying an overall assessment of the condition of 'significant benefit' and an individual assessment of the condition of 'clinical superiority'. In its view, the EU legislator considered both concepts to be substitutable in Regulation No 141/2000, with the result that there is no ground to consider that the concept of 'significant benefit' should be interpreted in a stricter way than the concept of 'clinical superiority'.

49 According to Mylan, the General Court adopted an incorrect interpretation according to which, although the overall balance of the three criteria relating to 'significant benefit' must be positive, it is sufficient for one of the three criteria relating to 'clinical superiority' to be fulfilled for a medicinal product to be considered clinically superior to another similar medicinal product.

50 Furthermore, a teleological interpretation of the derogation regime laid down in Article 8 of Regulation No 141/2000 also precludes such an interpretation. It is not in the interest of the relevant patients for a new medicinal product, with a negative overall benefit/risk balance compared to the existing medicinal product, to be placed on the market.

51 Furthermore, in Mylan's view, the General Court was wrong to endorse the Commission's reasoning that a generic medicinal product, such as Tobramycin VVB, can be clinically superior to an orphan medicinal product, such as Tobi Podhaler, despite the absence of any investment in research and development and despite the fact that such a generic medicinal product is merely a medicinal product similar to an existing medicinal product – in the present case, Tobi. In essence, according to Mylan, having regard to the interest of patients, which Regulation No 141/2000 seeks to protect, a medicinal product cannot be of significant benefit as compared to another while being clinically inferior to it.

52 Lastly, Mylan considers that the assessment of the concept of 'clinical superiority' set out in Article 3(3)(d) of Regulation No 847/2000 must include an overall evaluation. That provision defines a 'clinically superior' medicinal product as 'a medicinal product … shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways'. The words 'over and above' imply that the new medicinal product should be, from an overall perspective, better that the reference orphan medicinal product. This analysis should be carried out for the target population as a whole.

53 The Commission submits, in essence, that the first ground of appeal is a mere repetition of the arguments that Mylan relied on before the General Court and that it is therefore inadmissible. It also disputes, as does VVB, the merits of this ground of appeal.

Findings of the Court

54 As a preliminary point, as regards the plea of inadmissibility raised by the Commission, it follows from Article 256 TFEU and the first paragraph of Article 58 of the Statute of the Court of Justice of the European Union and also from Article 168(1)(d) and Article 169(2) of the Rules of Procedure of the Court that an appeal must indicate precisely the contested elements of the judgment which the appellant seeks to have set aside and the legal arguments specifically advanced in support of the appeal (judgment of 10 April 2014, *Acino* v *Commission*, C-269/13 P, EU:C:2014:255, paragraph 35 and the case-law cited).

55 Thus, where an appeal merely repeats or reproduces verbatim the pleas in law and arguments submitted to the General Court, including those based on facts expressly rejected by that Court, it fails to satisfy the requirements to state reasons under those provisions. Such an appeal amounts in reality to no more than a request for re-examination of the application submitted to the General Court, which the Court of Justice does not have jurisdiction to undertake (judgment of 10 April 2014, *Acino* v *Commission*, C-269/13 P, EU:C:2014:255, paragraph 36 and the case-law cited).

56 However, provided that an appellant challenges the General Court's interpretation or application of EU law, the points of law examined at first instance may be discussed again in the context of an appeal. Indeed, if an appellant could not thus base his appeal on pleas in law and arguments already relied on before the General Court, an appeal would be deprived of part of its purpose (judgment of 10 April 2014, *Acino* v *Commission*, C-269/13 P, EU:C:2014:255, paragraph 37 and the case-law cited).

57 In the present case, the first ground of appeal seeks, in essence, to call into question the General Court's interpretation of the concept of 'clinical superiority', for the purposes of Article 8(3)(c) of Regulation No 141/2000. In so doing, Mylan challenges a matter of law of the judgment under appeal with the result that that ground of appeal is admissible.

58 As to the substance, by that ground of appeal, Mylan alleges that the General Court erred in law by interpreting the concept of 'clinical superiority', set out in Article 8(3)(c) of Regulation No 141/2000, as meaning that it is sufficient for one of the criteria to be fulfilled in order to consider a given medicinal product clinically superior to an orphan medicinal product, which is inconsistent with the strict interpretation given to the concept of 'significant benefit', within the meaning of Article 3(1)(b) of that regulation.

59 In that regard, it must be borne in mind that the purpose of Regulation No 141/2000, according to Article 1 thereof, is to lay down a procedure at EU level for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products.

60 In order for a medicinal product to be designated as an 'orphan medicinal product', its sponsor must establish that the criteria laid down in Article 3 of that regulation are fulfilled. In particular, Article 3(1)(b) of that regulation establishes two situations which may lead to such a designation being obtained. Either the promoter demonstrates that there is no satisfactory method of

diagnosis, prevention or treatment of the condition in question, or if such a method exists, that sponsor must establish that the medicinal product will be of significant benefit to persons affected by that condition.

61 Article 3(2) of Regulation No 847/2000 defines the concept of 'significant benefit' as a clinically relevant advantage or a major contribution to patient care.

62 In addition, in its Notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products, the Commission stated that the concept of 'significant benefit' is part of legislation the purpose of which is to encourage and reward innovative treatments which require investment in research and in the development of potential improved medicinal products that can bring meaningful advantages for patients. In that light, the alternative criteria laid down in Article 3(2) of Regulation No 847/2000 on the basis of which it may be concluded that such a benefit exists must be interpreted strictly. As regards, in particular, the criterion relating to a 'major contribution to patient care', the Commission stated that, in order to satisfy that criterion, the product should at least be equivalent, in terms of efficacy, safety and benefit/risk balance, to similar medicinal products already authorised.

63 Once designation as an orphan medicinal product has been obtained, the marketing authorisation for that medicinal product confers entitlement, under the conditions laid down in Article 8 of Regulation No 141/2000, to market exclusivity. Under Article 8(1) of that regulation, where a marketing authorisation is granted for an orphan medicinal product, the European Union and the Member States are not, for a period of 10 years, to accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

64 Article 8(3) of that regulation nevertheless provides for three cases in which a similar medicinal product may be granted a marketing authorisation for the same therapeutic indication. According to Article 8(3)(c), that is the case, inter alia, when an applicant for such authorisation establishes that that medicinal product, which is similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

65 The concept of 'clinical superiority', within the meaning of that provision, is defined in Article 3(3)(d) of Regulation No 847/2000. Clinically superior means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways: it offers greater efficacy than the authorised orphan medicinal product; it offers greater safety in a substantial portion of the target population(s); or, in exceptional cases, it demonstrates a major contribution to diagnosis or to patient care.

66 It is apparent from the clear wording of that provision that the criteria for assessing the clinical superiority of a similar medicinal product over an orphan medicinal product, set out therein, are linked by the coordinating conjunction 'or', with the result that those criteria must be read as being alternative. It follows that it is sufficient that one of those criteria be fulfilled for the similar medicinal product concerned to be able to obtain a marketing authorisation by way of derogation from the market exclusivity enjoyed by the orphan medicinal product.

67 It is in the light of those considerations that the first ground of appeal is to be examined.

68 As regards, in the first place, the argument relating to the substitutability of the concepts of 'clinical superiority' and 'significant benefit', contrary to Mylan's assertions, the General Court, in the judgment under appeal, correctly identified the differences between those two concepts which preclude them from being regarded as interchangeable. Accordingly, in paragraph 115 of that judgment, it correctly acknowledged that those two concepts have different purposes and scope. It also noted, without erring in law, in paragraph 116 of that judgment, that, following amendments during the procedure for the adoption of Regulation No 141/2000, the EU legislature preferred the concept of 'significant benefit' as a criterion for designation as an orphan medicinal product and the concept of 'clinical superiority' as a criterion for derogating from market exclusivity. It correctly stated that this demonstrates the importance attached to the difference between those two concepts.

69 The General Court also correctly noted, in paragraphs 120 and 121 of the judgment under appeal, that those two concepts are based on the same assessment criteria and that those criteria are not cumulative either for the assessment of significant benefit or for the assessment of clinical superiority, as is apparent from the use of the coordinating conjunction 'or' both in Article 3(2) of Regulation No 847/2000 and in Article 3(3)(d) of that regulation.

70 The reference, in paragraph 124 of the judgment under appeal, to an 'overall evaluation of the benefit/risk balance' relates, as the Advocate General observed in points 66 and 67 of his Opinion, to the explanations set out in paragraphs 122 and 123 of the judgment under appeal. It follows from those explanations that, since, in this case, significant benefit was claimed on the basis of a major contribution to patient care for the entire target population, EMA and COMP required, in the process leading to the designation of Tobi Podhaler as an orphan medicinal product, that its safety and efficacy be at least equivalent to those of Tobi. In those circumstances, it was necessary to carry out such an overall assessment.

71 By contrast, the General Court's finding, in paragraph 132 of its judgment, that the clinical superiority criterion relied on in the present case for Tobramycin VVB, namely greater safety for a substantial portion of the target population(s), must be assessed individually, without establishing an overall benefit/risk balance for the population as a whole, was reached on a different basis. Indeed, Article 3(3)(d)(2) of Regulation No 847/2000 expressly establishes 'greater safety in a substantial portion of the target population(s)' as one of the criteria for the 'clinical superiority' required of the similar medicinal product. As the Advocate General observed, in essence, in points 69 to 72 of his Opinion, the clinical superiority of Tobramycin VVB over Tobi Podhaler had to be established by reference to greater safety for a subset of the target population, whereas the significant benefit in terms of ease of administration of Tobi Podhaler over Tobi and the equivalence in terms of safety and efficacy had to be established by reference to the entire target population. As a result, it was possible to conclude that, for a subset of the population concerned, Tobramycin VVB is safer than Tobi Podhaler, since it does not cause the adverse effects in question, and to conclude at the same time that the safety profile of those medicinal products for the entire population is equivalent.

72 It follows that, contrary to Mylan's assertions, there is no contradiction between paragraphs 124 and 132 of the judgment under appeal. While paragraph 124 of that judgment specifies certain specific features specific to the application of the criteria for assessing significant benefit, and more particularly to the criterion of 'major contribution to … care' brought about thereby, paragraph 132 of that judgment, for its part, sets out a conclusion specific to the assessment of the safety of a similar medicinal product in the context of the assessment of the clinical superiority of the latter.

73 As regards, in the second place, the argument relating to the objectives pursued by Regulation No 141/2000, Mylan states that it would be contrary to the objective of protecting the interests of patients to consider that a medicinal product is clinically superior to an orphan medicinal product when it is only the generic of the medicinal product in relation to which it has been demonstrated that the orphan medicinal product is of significant benefit. Such an interpretation would also be contrary to the objective pursued by that regulation, which is to create an incentive to invest in the research and development of orphan medicinal products.

74 In that regard, it should be noted, first, that, contrary to Mylan's assertions, it is in the interest of patients to have several therapeutic options available, even if the second is clinically superior only for a sub-category of patients. The derogations from market exclusivity provided for in Article 8(3) of Regulation No 141/2000 are designed precisely in line with that perspective, without calling into question the marketing authorisation granted for the orphan medicinal product.

75 In the present case, it is apparent from the judgment under appeal and from the decision at issue that Tobramycin VVB is a generic medicinal product of Tobi. Similarly, it has been established that Tobi Podhaler and Tobi have equivalent profiles when it comes to the overall assessment of their efficacy and safety. The General Court concluded in its absolute discretion that this was also the case for Tobramycin VVB. The significant benefit provided by Tobi Podhaler related, according to the judgment under appeal, to the speed and convenience of its administration. However, as the General Court noted, in essence, in paragraph 137 of that judgment, a substantial portion of the population suffering from cystic fibrosis and taking Tobi Podhaler suffered from a cough, which constituted a risk of discontinuation of treatment. It was for that subcategory of the target population that the Commission considered that Tobramycin VVB was safer than Tobi Podhaler, a view which the General Court endorsed, without it being possible to call that finding into question at the appeal stage.

76 Second, the derogations provided for in Article 8(3) of Regulation No 141/2000 cannot be regarded as contrary to the objective of encouraging research and development of orphan medicinal products. On the contrary, that provision gives concrete expression to the legislature's intention to safeguard patients' interest in having several therapeutic options where the generic medicinal product enjoying market exclusivity cannot be placed on the market in sufficient quantities or where there is a clinically superior medicinal product within the meaning of Article 8(3)(c) of that regulation.

77 In the third and last place, Mylan cannot rely on the wording of Article 3(3)(d) of Regulation No 847/2000 to claim that the assessment of the concept of 'clinical superiority' of a similar medicinal product must include an overall assessment of all the criteria set out. The expression 'over and above that provided by an authorised orphan medicinal product' cannot be artificially isolated from the remainder of the wording of that provision. That expression provides, in fact, that 'clinically superior' means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways. The list of the three alternative criteria, connected by the coordinating conjunction 'or', follows. It is therefore clear from the wording of that provision that the clinical superiority of a medicinal product is not assessed by means of an overall assessment of all the criteria provided for, but that it is sufficient for just one of those criteria to be fulfilled.

78 It follows from all the foregoing that the first ground of appeal must be rejected as unfounded.

The second ground of appeal

Arguments of the parties

79 By its second ground of appeal, Mylan criticises the General Court for failing, in paragraphs 137 to 139 of the judgment under appeal, to state sufficient reasons for its conclusion that the 10% threshold, used to assess the size of the target population, was reached.

80 Mylan does not dispute the fact that more than 10% of patients taking Tobi Podhaler experienced a cough or the fact that, for that reason, a cough was classified as a very common adverse effect of that medicinal product. However, Mylan is of the view that the General Court relied on insufficient reasoning to conclude that, because at least 10% of Tobi Podhaler patients suffered from a cough, Tobi and Tobramycin VVB ensured greater safety and a lower rate of discontinuation of treatment than Tobi Podhaler. The General Court did not explain why all or some of the patients suffering from a cough when taking Tobi Podhaler could potentially develop an intolerance.

81 The General Court failed to take into consideration more relevant facts and, in particular, the fact that only 3.9% of patients discontinued treatment with Tobi Podhaler due to a cough, which shows that the percentage of patients who develop an intolerance due to a cough is significantly less than 10%.

82 Furthermore, Tobi Podhaler produces fewer overall serious adverse effects than Tobi.

83 The Commission contends that the second ground of appeal must be rejected as unfounded in its entirety. Like the Commission, VVB disputes the merits of this ground.

Findings of the Court

84 It must be borne in mind that, according to settled case-law, the obligation to state reasons does not require the General Court to provide an account which follows exhaustively and one by one all the arguments put forward by the parties to the case, and that the General Court's reasoning may therefore be implicit, on condition that it enables the persons concerned to know why it has not upheld their arguments and provides the Court of Justice with sufficient material for it to exercise its power of review (see, to that effect, judgment of 4 July 2024, *Westfälische Drahtindustrie and Pampus Industriebeteiligungen* v *Commission*, C-70/23 P, EU:C:2024:580, paragraph 57 and the case-law cited).

85 In the present case, the General Court highlighted, in accordance with the conditions required by that case-law, the reasons justifying the superior safety of Tobramycin VVB as compared to Tobi Podhaler. In paragraphs 137 to 139 of the judgment under appeal, the General Court found, first, that the studies underlying the decision at issue demonstrated that, in all age groups, a cough occurred more frequently in patients taking Tobi Podhaler than in patients taking Tobi or Tobramycin VVB. It also noted that the rate of intolerance to Tobi Podhaler was higher than the rate of intolerance to Tobi and Tobramycin VVB. Second, still referring to those studies, the General Court held that there was a significant part of the target population which, in the light of the fact that a cough constituted a 'very common' adverse effect of Tobi Podhaler, could potentially have developed an intolerance justifying an alternative treatment to Tobi Podhaler. The General Court concluded that it was wrong to take into account only the rate of patients

who discontinued use of Tobi Podhaler because of the cough incidence (namely 3.9% of the total of patients treated with that medicinal product) when the rate of all patients potentially intolerant for this reason is more than 10% of that total. It noted that, in any event, that discontinuation rate was higher for Tobi Podhaler than for Tobi and Tobramycin VVB.

86 As regards Mylan's argument that only patients who discontinue using Tobi Podhaler should be regarded as intolerant to that medicinal product, it is sufficient to note that, in paragraphs 137 to 141 of the judgment under appeal, the General Court held that a patient may be intolerant to that medicinal product if he or she is exposed to adverse effects caused by the treatment which could be avoided by alternative treatment, as is apparent from the assessment reports on which the Commission relied.

87 It follows from the foregoing that the General Court gave sufficient reasons for its conclusion that the Commission had, in the decision at issue, correctly decided that Tobramycin VVB was clinically superior to Tobi Podhaler for a substantial portion of the target population.

88 Mylan's argument alleging insufficient reasoning is therefore unfounded.

89 As regards the assessment of the respective adverse effects of Tobi and Tobi Podhaler, it should be recalled that, according to settled case-law, in accordance with the second subparagraph of Article 256(1) TFEU and the first paragraph of Article 58 of the Statute of the Court of Justice of the European Union, the Court's jurisdiction in appeals brought against a decision of the General Court is limited to points of law, to the exclusion of any assessment of the facts. The General Court therefore has sole jurisdiction to assess the evidence. The assessment of that evidence does not therefore constitute, except in the case of its distortion, a question of law which is subject, as such, to review by the Court of Justice in the context of an appeal (see, to that effect, order of the Vice-President of the Court of 22 February 2022, *Fastweb* v *Commission*, C-649/21 P(I), EU:C:2022:171, paragraph 27 and the case-law cited).

90 By its line of argument set out in paragraph 22 of the appeal, according to which the General Court failed to take into consideration the most relevant facts, Mylan, in essence, merely calls into question, without invoking any distortion, the relevance of the evidence relied on by the General Court to conclude that, for a substantial portion of the target population, Tobramycin VVB was clinically superior to Tobi Podhaler. That line of argument is therefore inadmissible.

91 The second ground of appeal must therefore be rejected as being in part unfounded and in part inadmissible.

92 Having regard to all of the foregoing considerations, the appeal must be dismissed in its entirety.

Costs

93 In accordance with Article 184(2) of the Rules of Procedure, where the appeal is unfounded, the Court is to make a decision as to costs.

94 Under Article 138(1) of those rules, which applies to appeal proceedings by virtue of Article 184(1) thereof, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings.

95 Since the Commission, VVB and EMA have applied for costs to be awarded against Mylan and the latter has been unsuccessful, Mylan must be ordered to bear its own costs and to pay those incurred by the Commission, VVB and EMA.

On those grounds, the Court (Eighth Chamber) hereby:

1. Dismisses the appeal.

2. Orders Mylan IRE Healthcare Ltd to pay the costs.

Piçarra Jürimäe Gavalec

Delivered in open court in Luxembourg on 4 October 2024.

A. Calot Escobar
Registrar

N. Piçarra
President of the Chamber