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JUDGMENT OF THE GENERAL COURT (Seventh Chamber)
22 March 2018(*)

(Medicinal products for human use — Validation of an application for designation as an orphan medicinal product — Significant benefit — EMA decision refusing to validate an application for designation as an orphan medicinal product — Article 3(1)(b) and Article 5(1), (2) and (4) of Regulation (EC) No 141/2000)

In Case T-80/16,

Shire Pharmaceuticals Ireland Ltd, established in Dublin (Ireland), represented by D. Anderson QC, M. Birdling, barrister, G. Castle and S. Cowlishaw, solicitors,

applicant,

v

European Medicines Agency (EMA), represented by T. Jabłoński, N. Rampal Olmedo and M. Tovar Gomis, acting as Agents,

defendant,

supported by

European Commission, represented by K. Petersen and A. Sipos, acting as Agents,

intervener,

APPLICATION pursuant to Article 263 TFEU seeking the annulment of the EMA decision of 15 December 2015 refusing to validate the application submitted by Shire Pharmaceuticals Ireland for designation of Idursulfase-IT as an orphan medicinal product,

THE GENERAL COURT (Seventh Chamber),

composed of V. Tomljenović, President, E. Bieliūnas and A. Kornezov (Rapporteur), Judges,

Registrar: E. Coulon,

gives the following

Judgment

Background to the dispute

On 11 December 2001, the European Commission adopted a decision whereby 'iduronate-2-sulfatase', also commonly known as 'idursulfase', was designated as an orphan medicinal product for the treatment of mucopolysaccharidosis, type II (Hunter Syndrome) ('Hunter Syndrome' or 'MPS II') and was entered in the Register of Orphan Medicinal Products of the European Union pursuant to 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 designation decision of 2001').

On 8 January 2007, the Commission granted Shire Human Genetic Therapies AB a marketing authorisation ('MA') for the medicinal product Elaprase, containing the active substance idursulfase, for the treatment of Hunter Syndrome. Elaprase is administered as a concentrate that is made up into a solution for intravenous infusion.

In parallel, Shire group companies (collectively 'Shire'), which include Shire Human Genetic Therapies and the applicant, Shire Pharmaceuticals Ireland Ltd, started developing another medicinal product containing the same active substance, idursulfase, and making it possible to deliver that substance directly into the cerebrospinal fluid through intrathecal administration ('Idursulfase-IT') due to an unsatisfied clinical need for treatment of patients with Hunter Syndrome, namely those suffering from a severe form of that disease involving cognitive disorders. Shire has repeatedly expressed its intention to lodge an application for designation of that product as an orphan medicinal product with the European Medicines Agency (EMA).

By letters of 21 January and 17 March 2010, Shire asked the EMA for protocol assistance for the development of Idursulfase-IT, as suggested by the EMA in an email of 12 February 2009. The assistance requested was granted on 20 May 2010.

On 26 August 2013, the applicant submitted to the EMA an application for designation of Idursulfase-IT as an orphan medicinal product for the treatment of 'cognitive disease in MPS II patients' ('the 2013 application'). The applicant based its application on the premiss that the cognitive disorders that may arise with Hunter Syndrome constituted a distinct medical condition from Hunter Syndrome.

On 28 October 2013, the EMA informed the applicant of its refusal to validate the 2013 application, on the ground that the cognitive disorders that may arise with Hunter Syndrome, for the treatment of which a marketing authorisation relating to the medicinal product Elaprase had already been issued, did not constitute a distinct medical condition, but a severe form of that disease ('the 2013 decision'). The 2013 decision has not been challenged by the applicant.

On 17 September 2015, a meeting took place in the presence of representatives of the EMA and Shire about the intention of the latter to submit a new request for the designation of Idursulfase-IT as an orphan medicinal product, based this time on the premiss that it was a new product that would be of significant benefit in the treatment of Hunter Syndrome compared to existing treatments, including Elaprase, within the meaning of Article 3(1)(b) of Regulation No 141/2000. At that meeting, the EMA stated that since Idursulfase-IT contained the same active substance as that which was the subject of the designation decision of 2001, namely idursulfase, it was not able to validate that application.

On 25 November 2015, the applicant nonetheless submitted an application for designation of Idursulfase-IT as an orphan medicinal product, noting that the new medicinal product would be of significant benefit to patients affected by Hunter Syndrome within the meaning of Article 3(1)(b) of Regulation No 141/2000 ('the 2015 application').

By letter of 15 December 2015, the EMA refused to validate the 2015 application ('the contested decision'), stating that it did not comply with Article 5(1) of Regulation No 141/2000, on the following grounds:

the active substance idursulfase was granted an orphan designation for the treatment of Hunter Syndrome in 2001, and was authorised as orphan medicinal product Elaprase in January 2007 for the long-term treatment of patients with Hunter Syndrome;

the designation decision of 2001 refers in general terms to idursulfase without, however, specifying a particular form of administration; accordingly, the product which is the subject of the application, namely Idursulfase-IT, is covered by that designation and could only benefit from incentives deriving therefrom;

pursuant to Section C.1 of the Communication from the Commission on Regulation No 141/2000 (OJ 2003 C 178, p. 2, 'the 2003 communication'), 'in cases in which the therapeutic indication approved through the marketing authorisation procedure is a subset of the designated orphan condition, the marketing authorisation holder will benefit from market exclusivity for this product, for this indication. If the same sponsor subsequently applies for a marketing authorisation for a second subset of the designated orphan condition, the product will not benefit from any additional period of market exclusivity, for that second authorised indication, i.e. the second authorised indication will be covered by the market exclusivity granted on initial authorisation';

Shire had in May 2010 received assistance from the EMA for the development of a form of intrathecal idursulfase as part of the designation decision of 2001.

Procedure and forms of order sought

By application lodged at the Registry of the General Court on 23 February 2016, the applicant brought the present action.

On 20 May 2016, the EMA lodged its defence at the Court Registry.

By document lodged at the Court Registry on 25 May 2016, the Commission applied for leave to intervene in the present proceedings in support of the form of order sought by the EMA. By decision of 24 June 2016 the President of the Fourth Chamber of the General Court granted leave to intervene. The intervener lodged its statement in intervention and the main parties lodged their observations on that statement within the period prescribed.

The applicant lodged its reply at the Court Registry on 7 July 2016.

On 12 September 2016 the EMA lodged its rejoinder at the Court Registry.

By decision of the President of the General Court, the present case was assigned to a new Judge-Rapporteur sitting in the Seventh Chamber.

By letters of the Registry of 5 May 2017, the Court put written questions to the parties by way of measures of organisation of procedure. The parties duly replied to those questions within the allotted time.

Since no request for a hearing was submitted by the main parties within three weeks after service of notification of the close of the written part of the procedure, the Court has decided to rule on the action without an oral part of the procedure, pursuant to Article 106(3) of the Rules of Procedure of the General Court.

The applicant claims that the Court should:

annul the contested decision;

order the EMA to pay the costs.

The EMA and the Commission contend that the Court should:

dismiss the action as inadmissible;

in the alternative, dismiss the action as unfounded;

order the applicant to pay the costs.

Law

Admissibility

The EMA pleads the inadmissibility of the action on the ground that the contested decision is purely confirmatory of the 2013 Decision. In that regard, it states that the two decisions are based on Article 5(1) of Regulation No 141/2000 and on the same ground for refusal, namely that idursulfase had already been designated, in 2001, as an orphan medicinal product for the treatment of Hunter Syndrome. The contested decision does not include in its reasoning justifying the refusal of validation any new factor in relation to those contained in the 2013 Decision.

The applicant disputes the EMA's arguments.

According to settled case-law, a decision is a mere confirmation of an earlier decision where it contains no new factors as compared with the earlier measure and is not preceded by any re-examination of the situation of the addressee of the earlier measure (order of 29 April 2004, *SGL Carbon* v *Commission*, T-308/02, EU:T:2004:119, paragraph 51, and of 24 May 2011, *United Kingdom* v *Commission*, T-115/10, not published, EU:T:2011:242, paragraph 25).

However, the confirmatory or other nature of a measure cannot be determined solely with reference to its content as compared with that of the previous decision which it is said to confirm. It is also necessary to assess the nature of the contested measure in the light of the nature of the request to which it constitutes a reply (see judgment of 7 February 2001, *Inpesca* v *Commission*, T-186/98, EU:T:2001:42, paragraph 45 and the case-law cited, and order of 29 April 2004, *SGL Carbon* v *Commission*, T-308/02, EU:T:2004:119, paragraph 52 and the case-law cited).

In the present case, it must be held that the 2015 application was based on one of the designation criteria provided for in Article 3(1) of Regulation No 141/2000, different from that on which the 2013 application was based. Similarly, the 2013 decision and the contested decision were based, in part, on different grounds.

It should be noted in that regard that Article 3(1)(b) of Regulation No 141/2000 provides for alternative criteria for the designation of a medicinal product as an orphan medicinal product, which are that there is no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the [European Union] ('the designation criterion laid down in the first alternative of Article 3(1)(b) of Regulation No 141/2000'), or, if it exists, that the medicinal product will be of significant benefit to those affected by that condition ('the designation criterion laid down in the second alternative of Article 3(1)(b) of Regulation No 141/2000').

It is clearly apparent from the 2013 application that it was based on the premiss that the cognitive disorders which arise with Hunter Syndrome constituted a distinct disease from Hunter Syndrome itself for which there were no other previously authorised treatment methods. The email accompanying the 2013 application indicated that it concerned the treatment of 'cognitive disease in MPS II (Mucopolysaccharidosis II) patients' and, in point A.1 of the 2013 application, it was explained that some patients suffering from Hunter Syndrome were equally affected by a 'cognitive disease, with distinctive features that [required] a different treatment modality' and that that 'cognitive disease' was a 'distinct medical condition' from Hunter Syndrome. The applicant had stated, in its application, that it was submitting in that regard data capable of supporting those statements. In points D.1 and D.3 of that application, the sponsor had indicated that there were no other methods for the treatment of that cognitive disease and that, consequently, the criterion of 'significant benefit' was not applicable to its application. It can therefore be inferred that the 2013 application was based on the designation criterion laid down in the first alternative of Article 3(1)(b) of Regulation No 141/2000.

In the 2013 decision, the EMA noted that cognitive disease in MPS II patients was not a distinct disease from Hunter Syndrome but constituted a severe form of the latter. Therefore, the EMA took the view that the application could not be validated under Article 5(1) of Regulation No 141/2000, in so far as it was presented, for the same indication, after the MA for Elaprase.

By contrast, the 2015 application was based on the premiss that Idursulfase-IT was a new product that would provide a 'significant benefit' to patients with Hunter Syndrome compared to existing methods of treatments, including in relation to Elaprase, within the meaning of the second alternative of Article 3(1)(b) of Regulation No 141/2000. It is apparent from the letter accompanying the 2015 application and the table annexed thereto that, unlike the 2013 application, the orphan indication was described as 'Hunter Syndrome'. Furthermore, it is apparent from points D.1 and D.3 of the 2015 application that there was an approved treatment for that illness, namely Elaprase, and that the new medicinal product Idursulfase-IT would be of significant benefit compared to the first product.

This is also shown in the minutes of the meeting of 17 September 2015 (see paragraph 7 above), to which reference is made in the contested decision, from which it appears that the EMA was aware of Shire's intention to request the re-examination of the designation of Idursulfase-IT as an orphan medicinal product, invoking, this time, the existence of a potentially significant benefit deriving from that new product compared to existing treatment methods, including Elaprase. In addition, Shire stated during the meeting that that approach took account of the 2013 decision.

Thus, the contested decision, in contrast to the 2013 decision, was not motivated by the conclusion that the cognitive disorders did not constitute a medical condition distinct from Hunter Syndrome, but by the fact that the new product that Shire intended to develop, namely Idursulfase-IT, was already covered by the designation decision of 2001, which applied generally to the active substance idursulfase.

In those circumstances, the contested decision cannot be regarded as being purely confirmatory of that of 2013 and, accordingly, the plea of inadmissibility must be rejected.

Substance

Arguments of the parties

The applicant relies in support of its action on a single plea, alleging incorrect interpretation and application of Regulation No 141/2000. That plea is divided into six parts.

In the first part, the EMA is alleged not to have taken into account the merely procedural nature of the verification of the validity of the 2015 application. In the circumstances of the present case, since the 2015 application was submitted before the application for MA of Idursulfase-IT and was accompanied by the information and documents required under Article 5(2) of Regulation No 141/2000, the EMA was obliged to validate the application, pursuant to Article 5(4) of that Regulation. The sole effect of the validation decision was to trigger the procedure laid down in Article 5(5) to (8) of Regulation No 141/2000, in order to ascertain whether the designation criteria, laid down in Article 3(1) of that regulation, were met. In the contested decision, the EMA took account of elements which it should not have taken into account at a purely formal stage of the designation process, such as the validation of an application for designation. The question of whether the criteria for designation are satisfied falls to be considered not at the validation stage but in the following stage of the procedure, in accordance with Articles 5(5) to (8) of Regulation No 141/2000.

The second part, raised in the alternative, concerns the incorrect application by the EMA of the designation criteria of Idursulfase-IT as an orphan medicinal product.

In the third part, the applicant submits that the EMA incorrectly emphasised the fact that both Idursulfase-IT and Elaprase contain the same active substance. The 'active substance' concept is different from that of 'medicinal product', the former concept relating to only one of the components, amongst others, of a medicinal product. Thus, the fact that the active substance of Idursulfase-IT is also the active substance of Elaprase is of no legal significance for the purposes of the designation of a medical product as an orphan product, given that, as in the present case, they are distinct medicinal products.

In the fourth part, the applicant argues that the contested decision is based incorrectly on Section C.1 of the 2003 communication, since that section concerned the issue of an MA and not the designation criteria of a medicinal product as an orphan medicinal product under Article 3(1) of Regulation No 141/2000, or the validation criteria for an application for designation as an orphan medicinal product within the meaning of Article 5(4) of that regulation.

In its fifth part, the applicant claims that, in the circumstances of the present case, the fact that it had received protocol assistance for Idursulfase-IT in 2010 from the EMA does not mean that it had waived its right to obtain the status of orphan medicinal product for that medicinal product.

The sixth part, which, according to the applicant, supports the other parts of the single plea, alleges disregard for the objectives of Regulation No 141/2000. The applicant submits that the contested decision jeopardises the objective of Regulation No 141/2000 which seeks to encourage research, development and marketing of orphan medicinal products, since it refuses the validation even of the application for designation of Idursulfase-IT as an orphan medicinal product, thereby depriving the applicant of the opportunity to demonstrate, in substance, that that medicinal product would be of significant benefit to patients suffering from Hunter Syndrome within the meaning of the second alternative of Article 3(1)(b) of Regulation No 141/2000 even though the applicant developed that medicinal product by conducting own research and devoting major investments thereto.

The EMA, supported by the Commission, contends, first, that the verification of an application for designation of a medicinal product as an orphan medicinal product under Article 5(4) of Regulation No 141/2000 consists of checking that the particulars and documents required under Article 5(2) of that regulation have been delivered and that no application for an MA has been submitted previously. However, in the present case, the sponsor, the active substance and the therapeutic indication set out in the 2015 application were identical to those mentioned in the designation decision of 2001. Thus, Idursulfase-IT is covered by the designation decision of 2001. Since the operative part of the designation decision of 2001 refers in general terms to 'iduronate-2-sulfatase', the Commission cannot adopt a second decision with the same operative part.

In addition, in the judgment of 9 September 2010, *CSL Behring* v *Commission and EMA* (T-264/07, EU:T:2010:371), the General Court rejected the action for annulment of a decision refusing to validate an application for designation as an orphan medicinal product on the ground that the applicant was the holder of a marketing authorisation for the medicinal product in question, thus recognising that the EMA was entitled to refuse validation if certain conditions are not met.

Secondly, the EMA argued that it did not, in the contested decision, contrary to what the applicant claims, find that the conditions for designation of Idursulfase-IT as an orphan medicinal product were not met.

Thirdly, although it is true that Articles 3 and 5 of Regulation No 141/2000 refer to the concept of 'medicinal product', the fact remains that the 'active substance' is crucial to the interpretation of the term 'medicinal product'. The 2007 Elaprase MA did not change the scope of the designation decision of 2001, whose scope is broader than the marketing authorisation. At the time of the application for designation of the medicinal product as an orphan product, that product is, in principle, at an early stage of development, as a result of which its concentration, formulation or pharmaceutical form, which are to be used in humans, are not yet defined.In the present case, the original orphan designation was drafted and entered in the Register of Orphan Medicinal Products of the European Union under number EU/3/01/078 as follows: '"Iduronate-2-sulfatase" was designated as an orphan medicinal product for: treatment of mucopolysaccharidosis, type II (Hunter Syndrome)'.

In its replies to the measures of organisation of procedure, the EMA states that, in its view, the active substance, the sponsor and the orphan indication are the elements that make it possible to identify the medicinal product designated. The Commission further states in that regard, referring to the Opinion of Advocate General Bobek in Joined Cases *Novartis Europharm* v *Commission* (C-629/15 P and C-630/15 P, EU:C:2016:1003), that a distinction must be made between the constituent elements and the variable elements of a marketing authorisation for a medicinal product, abovementioned elements being, according to the Commission, the constituent components of a medicinal product. The same approach should be followed in the present case.In addition, the EMA claims that any further developments and improvements of the authorised medicinal product could then be covered by the initial orphan designation.In the present case, the differences in composition between Elaprase and Idursulfase-IT are insignificant and are intended to adjust the latter to intrathecal administration. Thus, Idursulfase-IT should instead be the subject of a possible request for the extension of the marketing authorisation for Elaprase, pursuant to Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and Annex I to that regulation (OJ 2008 L 334, p. 7), by way of amendments to the dosage and means of administration.

The EMA and the Commission further state that, referring to Article 2(4)(b) 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), that if another sponsor had submitted the same application for designation, that is a request relating to the designation of Idursulfase-IT as an orphan medicinal product for the treatment of Hunter Syndrome, the EMA would have validated it, provided that the requirements laid down in Article 5(1) and (2) of Regulation No 141/2000 had been met. However, such a differential treatment of sponsors is not contrary to the principle of equal treatment, since another sponsor would be in a different situation from that in which the applicant finds itself.

Fourthly, the EMA states that the contested decision is based on Article 5(1) of Regulation No 141/2000 and not on Section C.1 of the 2003 Communication. It states, however, that the reference to the latter is correct and relevant, in so far as any application for designation as an orphan medicinal product is formulated in the hope of subsequently being able to obtain a marketing authorisation.

Fifthly, the contested decision mentions the fact that, in 2010, Shire had obtained protocol assistance for Idursulfase-IT only in order to show that that medicinal product fell within the scope of the designation decision of 2001. It states, however, that the contested decision was not based on that fact.

Finally, according to the EMA, the grant of multiple designations for the same active substance in order to subsequently obtain an additional period of market exclusivity for the development of products for the same orphan therapeutic indication could create an incentive being misused to delay the marketing of improved products until expiry of the market exclusivity period for the first development, which is not in the interest of patients suffering from rare diseases. The applicant cannot, therefore, be granted a 'duplication' of market exclusivity, because that would amount to misuse of the provisions of Regulation No 141/2000.

Findings of the Court

It is appropriate to examine together the arguments put forward in the six parts of the single plea, alleging incorrect interpretation and application of Regulation No 141/2000, in so far as they concern, in essence, an infringement by the EMA of Article 5(1), (2) and (4) of that regulation and of the objectives underpinning it.

It should be noted at the outset that Regulation No 141/2000 lays down specific, separate procedures for, on the one hand, the designation of medicinal products as orphan medicinal products and, on the other, the marketing authorisations of those medicinal products.

The procedure for the designation of medicinal products as orphan medicinal products, at issue in the present case, takes place in several stages. As a first step, the sponsor is to submit, under Article 5(1) of Regulation No 141/2000, an application to the EMA, at any stage of the development of the medicinal product, but before the application for the marketing authorisation. Article 5(2) of Regulation No 141/2000 contains the exhaustive list of information and documents that must accompany the application, namely: first, the name or corporate name and permanent address of the sponsor; secondly, the active ingredients of the medicinal product; thirdly, the proposed therapeutic indication; and, fourthly, evidence that the criteria laid down in Article 3(1) of that regulation are met and a description of the stage of development, including the indications expected.

The EMA is required to verify, at this stage of the proceedings, the validity of the application, pursuant to Article 5(4) of Regulation No 141/2000. Thus, it must check, on the one hand, whether the application was submitted at any stage of the development of the medicinal product before the application for marketing authorisation was made, as required by Article 5(1) of that regulation and, on the other, whether the application is accompanied by the information and documents referred to in Article 5(2) of the regulation. Following that verification, the EMA may, where appropriate, request the sponsor to supplement the particulars and documents accompanying the application. If the application complies with the requirements laid down in Article 5(1) and (2) of Regulation No 141/2000, the EMA is obliged to validate and transmit it, next, to the Committee on Orphan Medicinal Products.

The verification of the validity of applications by the EMA under Article 5(4) of Regulation No 141/2000 is therefore purely administrative in nature, a matter on which the parties to the present proceedings expressly agreed.

It is only at the second stage that the Committee on Orphan Medicinal Products is to adopt, pursuant to Article 5(5) to (7) of Regulation No 141/2000, an opinion on the question whether the medicinal product covered by the application for designation as an orphan medicinal product meets the criteria set out in Article 3(1) of that regulation, namely, in particular, whether the medicinal product will be of significant benefit to patients affected by a condition for which a satisfactory method of treatment had been authorised. It is ultimately for the Commission to adopt a decision on the designation of a medicinal product as an orphan medicinal product, in accordance with Article 5(8) of Regulation No 141/2000. Under Article 5(9) of that regulation, the designated medicinal product shall be entered in the Register of Orphan Medicinal Products of the European Union.

In the present case, it is not disputed that the contested decision is not based on an infringement of Article 5(2) of Regulation No 141/2000. However, the EMA refused to validate the 2015 application on the ground that the applicant had already obtained, in 2001, an orphan designation for idursulfase for the treatment of Hunter Syndrome and that a marketing authorisation had been granted in 2007 for the orphan medicinal product Elaprase, as a result of which the application did not satisfy the requirement laid down in Article 5(1) of Regulation No 141/2000 that it must be submitted 'at any stage of the development of the medicinal product before the application for marketing authorisation'.

In that regard, it should be noted, first, that, at the time that the 2015 application was lodged, Idursulfase-IT was still under development and that no application for marketing authorisation had been submitted in respect thereof, which is, moreover, not disputed by the parties.

Secondly, it is necessary to ascertain whether the fact that the applicant had already obtained marketing authorisation for the orphan medicinal product Elaprase — containing the same active substance as that contained in

Idursulfase-IT — for the treatment of Hunter Syndrome prevented the validation of the 2015 application on the ground that the condition laid down in Article 5(1) of Regulation No 141/2000 was not satisfied.

In that regard, it must be observed that the sole fact that both Idursulfase-IT and Elaprase contain the same active substance does not necessarily mean that they are the same medicinal product.

As the applicant correctly notes, the terms 'medicinal product' and 'active substance' cover two different concepts. The term 'medicinal product' is defined in Article 1(2) of Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ 2001 L 311, p. 67), referred to in Article 2(a) of Regulation No 141/2000, read in conjunction with Article 128 of that directive. According to the definition, 'any substance or combination of substances presented as having properties for treating or preventing disease in human beings' or 'any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis' is a 'medicinal product' (see, to that effect, judgment of 10 July 2014, *D. and G.*, C-358/13 and C-181/14, EU:C:2014:2060, paragraph 27).

The term 'active substance' is defined in Article 1(3a) of Directive 2001/83 as 'any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis'.

Moreover, as the applicant submits, without being contradicted on that point by the EMA, a medicinal product also contains, in addition to one or more active substances, excipients, which are defined in Article 1(3b) of Directive 2001/83 as 'any constituent of a medicinal product other than the active substance and the packaging material'.

It follows that, if the active substance is indeed one of the components or the main constituent of a medicinal product within the meaning of the applicable legislation (see paragraphs 58 and 59 above), it must not be confused with the medicinal product itself.

In the present case, it is apparent from the file before the Court, in particular the 2015 application, that Elaprase differs from Idursulfase-IT in its composition, method of administration and therapeutic effects. As regards the composition of Idursulfase-IT, it is common ground between the parties that, although it contains the same active substance as Elaprase, their respective compositions differ in that the former medicinal product contains only three of the five excipients contained in the latter. As regards the envisaged administration of Idursulfase-IT, it is carried out by means of an implantable port placed beneath the skin into which the medicinal product is injected, and a catheter that connects the port to the spinal canal, thus enabling health professionals to administer it regularly without having to introduce a needle into the patient's spinal canal. Idursulfase-IT could, unlike Elaprase, cross the blood-brain barrier and reach the patients' brain.

As regards its therapeutic effects, according to the data in the 2015 application, Idursulfase-IT would allow the cognitive disorders exhibited by some of the patients suffering from Hunter Syndrome to be treated. Those patients usually have a life expectancy of one or two decades, while patients with the same illness, but suffering only from somatic disorders generally have a longer life expectancy, namely two or three decades. Although Elaprase is effective in combating somatic disorders, it is not effective in respect of cognitive disorders which arise in patients suffering from a severe form of Hunter Syndrome. Thus, according to the 2015 application, Idursulfase-IT would not replace Elaprase, but would constitute a supplementary treatment for patients suffering from cognitive disorders, which is furthermore confirmed by the contested decision which mentions that Idursulfase-IT would be administered 'in conjunction with' Elaprase.

In view of the above, it does not appear, at the validation stage of the 2015 application, that Idursulfase-IT is the same medicinal product as Elaprase. The question whether the differences referred to in paragraphs 62 and 63 above are 'insignificant' as argued by the EMA is a scientific matter which is not subject to the review of the validity of an application for designation as an orphan medicinal product under Article 5(4) of Regulation No 141/2000.

In those circumstances, the EMA could not refuse to validate the 2015 application on the ground that the applicant had obtained a marketing authorisation for the orphan medicinal product Elaprase.

Thirdly, as regards the argument referred to in the contested decision, according to which the designation decision of 2001 related in general to the active substance idursulfase, without further specifics, as a result of which that decision also covered the medicinal product which was the subject of the 2015 application, it should be noted that it is quite normal that, where an application for designation as an orphan medicinal product has been submitted at the stage of the development of a medicinal product, it is described in respect of its active substance, upon which the parties agree. It is only at a later stage of its development that the medicinal product at issue becomes tangible for the purposes of its future marketing. Thus the designation decision of 2001, relating to the active substance idursulfase, led to the development of the medicinal product Elaprase containing that active substance. However, accepting that a designation originally formulated, at the stage of the development of a medicinal product, broadly and in respect of an active substance without further specification, could prevent any subsequent request for the designation of a new medicinal product containing the same active substance, and thus at the validation stage of such an application, would run counter to Article 3(1)(b) of Regulation No 141/2000 and to the objective and general scheme of that regulation.

Indeed, it follows neither from the wording of Article 5 of Regulation No 141/2000, on which the contested decision is based, nor from the context in which that provision occurs, nor from the general scheme of the regulation, that a sponsor cannot apply for designation as an orphan medicinal product of a medicinal product containing the same active substance as another product authorised in its own name for the same indication, provided that it can demonstrate, as

required by Article 5(2)(d) of Regulation No 141/2000 that the criterion for designation laid down in the second alternative of Article 3(1)(b) of Regulation No 141/2000 is met.

In that regard, it is apparent from the second alternative of Article 3(1)(b) of Regulation No 141/2000 that a medicinal product may be designated as an orphan product even if a treatment exists for the condition in question, provided that it represents a significant benefit to those affected by the condition (judgment of 22 January 2015, *Teva Pharma and Teva Pharmaceuticals Europe* v *EMA*, T-140/12, EU:T:2015:41, paragraph 64). Establishing significant benefit 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 (judgment of 9 September 2010, *Now Pharm* v *Commission*, T-74/08, EU:T:2010:376, paragraph 43).

The concept of 'significant benefit' is further explained in the 2003 communication, which is applicable to the circumstances of the present case. At no point does the wording thereof suggest that a potential medicinal product containing the same active substance as a previously authorised medicinal product in the name of the same sponsor could not be of significant benefit to patients suffering from the orphan disease in question. On the contrary, it is apparent from Section A.4 of that communication that several medical or other considerations could show that the medicinal product is of significant benefit within the meaning of the second alternative of Article 3(1)(b) of Regulation No 141/2000, such as, for example, an increased supply and availability of the method or ease of self-administration. Moreover, that communication expressly states that 'particular benefits for a sub-sample of the population' can provide a significant benefit. Similarly, it states that 'where there are serious and documented difficulties with the formulation or route of administration of an authorised medicinal product, a more convenient formulation or route may be considered as a significant benefit'.

It follows that the justification referred to in Article 5(2)(d) of Regulation No 141/2001, which refers in particular to the 'significant benefit' within the meaning of Article 3(1)(b), may be based on the assumption of a more efficient formulation and means of administration than an authorised medicinal product with the same active substance and intended to treat the same condition.

In the present case, it is specifically that assumption of 'significant benefit' on which the applicant based the 2015 application. Indeed, that application states that Idursulfase-IT would provide a significant benefit within the meaning of the second alternative of Article 3(1)(b) of Regulation No 141/2000 to persons suffering from Hunter Syndrome, compared to Elaprase, on account of its therapeutic effects as well as its composition and means of administration (see paragraphs 58 to 63 above).

Thus, it is the responsibility of the Committee on Orphan Medicinal Products to assess whether the characteristics of Idursulfase-IT are likely to be of significant benefit to patients suffering from the condition at issue within the meaning of the second alternative of Article 3(1)(b) of Regulation No 141/2000, taking into account the relevant scientific evidence, in accordance with Article 4(2) of that regulation.

In addition, it is apparent from an extract of the Register of Orphan Medicinal Products of the European Union, as submitted by the applicant as part of the present proceedings,that a designation in that register may include additional specifications for the medicinal product beyond the active substance, including the intended method of administration, which could allow, for the purposes of the validation of the application, the individualisation of that medicinal product in relation to the designation decision of 2001, so that the operative parts of the two decisions are different.

Fourthly, in so far as the contested decision also refers to Section C.1 of the 2003 communication and to the fact that, in May 2010, Shire received protocol assistance from the EMA for the development of Idursulfase-IT under the 2001 Decision, it should be noted that the EMA itself acknowledged, in its defence and in its replies to the measures of organisation of procedure, that the contested decision was not based on any of those considerations. On the one hand, Section C of the 2003 Notice concerns the application of Article 7(3) of Regulation No 141/2001, a provision which was not used as the basis of either the 2015 application or the contested decision. On the other hand, the EMA itself has conceded that the protocol assistance it gave for the development of Idursulfase-IT 'was not the basis for the contested decision' and that 'there was no eligibility test and no waiving of any rights'.

Fifthly, it must be stated that none of the arguments put forward by the EMA and by the Commission in the present case is such as to justify the contested decision.

As regards, first, the argument that the EMA derives from the judgment of 9 September 2010, *CSL Behring* v *Commission and EMA* (T-264/07, EU:T:2010:371), it is sufficient to note that the circumstances which gave rise to that judgment differ significantly from those of the present case. The medicinal product covered by the application for designation at issue in the case which gave rise to that judgment was identical to that already authorised on the markets of several Member States, whereas, in the present case, the 2015 application was based on the premiss that Idursulfase-IT was objectively different from Elaprase.

As regards, secondly, the EMA's argument that the Applicant should instead seek, in relation to Idursulfase-IT, an extension of the MA granted for Elaprase within the meaning of Annex I to Regulation No 1234/2008, it is sufficient to note that the 2015 application did not concern the placing on the market of Idursulfase-IT, a potential medicinal product which was, at that time, still at the development stage. The question of what MA procedure should subsequently be followed is therefore both premature and irrelevant in order to check the validity of the 2015 application.

Thirdly, with respect to the Commission's argument based on the Joined Cases in *Novartis Europharm* v *Commission* (C-629/15 P and C-630/15 P, EU:C:2017:498), it must be observed that it concerned in particular the interpretation of

the concept of 'global marketing authorisation' within the meaning of Article 6(1) of Directive 2001/83 and the regulatory data protection period within the meaning of Article 10(1) of that directive. As was pointed out in paragraph 77 above, the present case does not concern an MA application in respect of the medicinal product at issue, but an application for designation as an orphan medicinal product, Regulation No 141/2000 providing in that regard for separate and distinct procedures concerning each of those applications, as the Court recalled in paragraph 49 of the present judgment. The procedure for designation as an orphan medicinal product is subject, inter alia, to criteria such as 'significant benefit' which are specific to the system established by Regulation No 141/2000. Therefore, the 'global marketing authorisation' concept at issue in the judgment of 28 June 2017, *Novartis Europharm* v *Commission* (C-629/15 P and C-630/15 P, EU:C:2017:498), is not relevant to the determination of the present case.

Fourthly, as regards the EMA's argument based on Article 2(4)(b) of Regulation No 847/2000, it is sufficient to note that that provision applies to the 'same medicinal product', whereas, in the present case, given the differences between Idursulfase-IT and Elaprase it does not appear, at the validation stage of the 2015 application, that the same medicinal product is at issue, as was pointed out in paragraph 64 of the present judgment.

Finally, as regards the EMA's argument that a possible 'duplication' of trade exclusivity 'would lead to a misuse of the provisions of [Regulation No 141/2000] and would be contrary to its purpose', it must be borne in mind that, according to well-established case-law, evidence of an abusive practice requires, first, a combination of objective circumstances in which, despite formal observance of the conditions laid down by the EU rules, the purpose of those rules has not been achieved, and, second, a subjective element consisting in the intention to obtain an advantage from the EU rules by artificially creating the conditions required for obtaining it (see judgment of 16 October 2012, *Hungary* v *Slovakia*, C-364/10, EU:C:2012:630, paragraph 58 and the case-law cited).

However, where, a medicinal product meets the criteria for designation as an orphan medicinal product, criteria laid down in Article 3(1) of Regulation No 141/2000, including where that product contains the same active substance as another medicinal product already designated as an orphan product, it must itself be designated an orphan medicinal product. It is in the interest of patients suffering from a rare disease to have access to a similar medicinal product giving them a significant benefit compared to a previously authorised orphan product (see, to that effect, judgment of 3 March 2016, *Teva Pharma and Teva Pharmaceuticals Europe* v *EMA*, C-138/15 P, not published, EU:C:2016:136, paragraph 28).

Moreover, the fact that an orphan medicinal product enjoys the period of market exclusivity provided in Article 8(1) of Regulation No 141/2000 does not preclude a second, similar product which has been authorised pursuant to Article 8(3) of that regulation being granted, in turn, market exclusivity, as long as it also fulfils the requirements set out in Article 3(1) of the regulation for designation as an orphan medicinal product (see, to that effect, judgment of 3 March 2016, *Teva Pharma and Teva Pharmaceuticals Europe* v *EMA*, C-138/15 P, not published, EU:C:2016:136, paragraph 32). It should be noted in that regard that, in accordance with Article 3(3)(b) and (c) of Regulation No 847/2000, two medicinal products dealing with the same disease and containing the same active substance may be regarded as 'similar medicinal products' for the purposes of the application of Article 8 of Regulation No 141/2000. It is equally irrelevant, for the purposes of applying Article 8(3) of Regulation No 141/2000, that the holder of the marketing authorisation for the original orphan medicinal product and the sponsor of the second product are the same pharmaceutical company (judgment of 22 January 2015, *Teva Pharma and Teva Pharmaceuticals Europe* v *EMA*, T-140/12, EU:T:2015:41, paragraph 77). Consequently, it cannot be held that the potential designation of Idursulfase-IT as an orphan medicinal product, if the relevant conditions are met, would lead, in a future marketing authorisation, to any 'duplication' of market exclusivity or that it would run counter to the objective pursued by Regulation No 141/2000.

On the contrary, the argument advanced by the EMA and the Commission would lead to a sponsor such as the applicant being deprived of any opportunity to demonstrate scientifically that its product entails significant benefit to patients suffering from the condition at issue within the meaning of the second alternative of Article 3(1)(b) of Regulation No 141/2001.

Consequently, in the light of all the foregoing considerations, the single plea must be upheld and the contested decision annulled.

Costs

Under Article 134(1) 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 EMA has been unsuccessful, it must be ordered to pay the applicant's costs, in accordance with the form of order sought by the applicant.

In accordance with Article 138(1) of the Rules of Procedure, the Commission, intervener in the present proceedings, is to bear its own costs.

On those grounds,

THE GENERAL COURT (Seventh Chamber)

hereby:

Annuls the decision of the European Medicines Agency (EMA) dated 15 December 2015 refusing to validate the application submitted by Shire Pharmaceuticals Ireland Ltd seeking the designation of Idursulfase-IT as an orphan medicinal product;

Orders the EMA to bear its own costs, as well as those of Shire Pharmaceuticals Ireland;

Orders the European Commission to bear its own costs.

Tomljenović Bieliūnas Kornezov

Delivered in open court in Luxembourg on 22 March 2018

E. Coulon S. Frimodt Nielsen

Registrar President

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* Language of the case: English.