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Shire v EMA. The European General Court clarifies the definition of medicinal product for orphan designation

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On 22 March 2018 the General Court of the European Union ('General Court') handed down its judgment in Case T-80/16, *Shire Pharmaceuticals Ireland Ltd* v *European Medicines Agency (EMA)*, restating its approach already taken in its judgement of 22 January 2015, Case T-140/12, *Teva Pharma BV*, *Teva Pharmaceuticals Europe BV* v *European Medicines Agency (EMA)* ('Teva v EMA') with regard to the orphan designation of a medicinal product.

Idursulfase, a medicinal product produced by *Shire Human Genetic Therapies AB* for the treatment of Hunter Syndrome, obtained the orphan designation on 11 December 2001. In 2007 the European Commission granted a marketing authorization ('MA') for the medicinal product Elaprase, containing the active substance idursulfase. Meanwhile, the *Shire Group Companies* ('Shire') had started developing another medicinal product containing the same active substance, *i.e.* idursulfase, 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 suffering from severe forms of that disease involving cognitive disorders. On 25 November 2015, Shire submitted an application for designation of Idursulfase-IT as an orphan medicine, noting that the new 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 on orphan medicinal products[1]. By letter of 15 December 2015, the EMA refused to grant the 2015 application ('the contested decision'), noting that:

- the active substance idursulfase had been granted an orphan designation for the treatment of Hunter Syndrome in 2001, and product Elaprase was authorised as orphan medicine 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 object of the 2015 application, namely Idursulfase-IT, is already covered by that designation and could only benefit from incentives deriving therefrom.

By application lodged at the Registry of the General Court on 23 February 2016, Shire asked the Court to annul the EMA decision of 2015 denying the orphan designation to Idursulfase-IT.

The General Court notes that Regulation No 141/2000 lays down specific, separate procedures for, on the one hand, the designation of medicinal products as orphan medicines and, on the other, the marketing authorisations of those medicines. In the instant case, the EMA refused 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 medicinal product Elaprase

[1] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. OJEU L 18 of 22.01.2000.

accordingly. Therefore, the application did not satisfy the requirement laid down in Article 5(1) of Regulation No 141/2000. The General Court recalls that, at the time 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 not disputed. It is therefore necessary to ascertain whether the fact that the applicant had already obtained a marketing authorisation for the orphan medicinal product Elaprase containing the same active substance for the treatment of Hunter Syndrome prevented grant 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[2]. Elaprase differs from Idursulfase-IT in its composition (the two products contain the same active substance but different excipients), method of administration and therapeutic effects. In particular, 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 to two decades, while patients with the same illness, but suffering only from somatic disorders generally have a longer life expectancy, namely two to three decades. In consequence, at the validation stage of the 2015 application, it does not appear that Idursulfase-IT is the same medicinal product as Elaprase. In those circumstances, the EMA could not refuse to grant the 2015 application on the ground that the applicant had obtained a marketing authorisation for Elaprase.

According to the General Court, it follows from neither 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 operates, nor from the general structure 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 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.

The General Court ends its analysis with a reference to its judgment Teva v EMA, pursuant to which a medicinal product may be designated as an orphan product even if a treatment exists for the condition that is at stake, provided that it

[2] See paragraph 58 of the judgment: "… *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)*…".

represents a significant benefit to those affected thereby[3]. Moreover, where a medicinal product meets the criteria for designation as an orphan medicine laid down in Article 3(1) of Regulation No 141/2000, it must be designated as an orphan medicine also when the product contains the same active substance as another medicine product already designated as an orphan 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[4]; the fact that an orphan medicine 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 from being granted, in turn, market exclusivity, as long as it also fulfils the requirements set out in Article 3(1) of the Regulation. 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.

On those grounds, the General Court annulled the EMA decision of 15 December 2015 refusing the application submitted by Shire seeking the designation of Idursulfase-IT as an orphan medicinal product.

The judgment in the Shire case reaffirms the principles set by the General Court and upheld by the Court of Justice in the Teva v EMA case with regard to the criteria to designate a product as an orphan medicinal product. In doing so, it is worthwhile noting that the General Court has taken a less restrictive approach in defining what a medicinal product is and in identifying how to differentiate medicinal products based on the same active substance, compared to the case law relative to Supplementary Protection Certificates (SPCs) and, more particularly, multiple SPCs.

In the Shire case, the Court held that "… *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*

[3] See paragraph 68 of the judgment: "… *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)*…".

[4] See paragraph 81 of the judgment.

27)… Moreover … 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…"[5]. Conversely, with regard to multiple SPCs, the Court held that "… *it cannot be accepted that the holder of a basic patent in force may obtain a new SPC, potentially for a longer period of protection, each time he places on the market in a Member State a medicinal product containing, on the one hand, an active ingredient, protected as such by the holder's basic patent and constituting the subject-matter of the invention covered by that patent, and, on the other, another substance which does not constitute the subject-matter of the invention covered by the basic patent*…"[6].

The SPC Regulation[7] is intended to re-establish a sufficient period of effective protection of a basic patent by permitting the holder to enjoy an additional term of exclusivity on its expiry, as a compensation, at least in part, for the delay in the commercial exploitation of the invention because of the time elapsed between the date on which the application for that patent was filed and the date on which the first marketing authorisation in the European Union was granted. The orphan medicinal products Regulation, on the other hand, was adopted to incentivize the pharmaceutical industry to develop medicinal products for rare conditions that occur so infrequently that the cost of bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the product.

The goals and interests underlying either Regulation are, therefore, clearly different. The case-law that has been produced on the SPC Regulation[8] tends to increasingly restrict supplementary protection by the filing or grant of multiple SPC's originated by the same basic patent, not infrequently at the expense of consistency with the patent legislation and the EPC system, fundamentally with the intent not to delay generic entry alongside off-patent medicines and, in that way, ease pressure on public pharmaceutical spend and the financial burden that is placed on national health services and public insurance schemes. An adverse effect of a restrictive SPC case-law is, though, an extent of de-incentivization of research on major diseases (such as HIV, cancer, Alzheimer, Parkinson, etc.)

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[5] See CJEU 22.03.2018, T-80/16, *Shire Pharmaceuticals Ireland Ltd* v *European Medicines Agency (EMA)*, paragraphs 58-61.

[6] See CJEU 12.03.2015, Case C-577/13, *Actavis Group PTC EHF, Actavis UK Ltd v Boehringer Ingelheim Pharma GmbH & Co. KG,* paragraph 37. See also CJEU 12.12.2013, Case C-433/12, *Actavis Group PTC and Actavis UK v Sanofi*, paragraph 30.

[7] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products. OJEU L 152 of 16.6.2009.

[8] See CJEU 12.03.2015, Case C-577/13, *Actavis Group PTC EHF, Actavis UK Ltd v Boehringer Ingelheim Pharma GmbH & Co. KG*, paragraph 39; CJEU 12.12.2013, Case C-433/12, *Actavis Group PTC and Actavis UK v Sanofi*, paragraph 43. CJEU 04.05.2006, Case C-431/04, *Massachusetts Institute of Technology*, paragraph 23.

which entail very long R&D and regulatory time frames and extremely huge investments that may be incapable of recovering within the limited period of exclusivity afforded by the basic patent and a conservative SPC policy. On the contrary, orphan medicines, that would not be commercially viable absent the incentives supplied by the special exclusivity period, seem to justify a more liberal regulatory approach, also considering that the “rare nature” of the diseases at stake is unlikely to make much difference in terms of reimbursement and pharmaceutical spend.