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Significant European Court Judgment for Developers of Orphan Medicines

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Life Sciences

European General Court confirms that a new medicinal product containing the same active substance as a company's existing medicinal product may be entitled to its own period of orphan exclusivity.

On 22 March 2018, the European General Court handed down its judgment in Case T-80/16 Shire Pharmaceuticals Ireland v. EMA, in which Covington represented Shire Pharmaceuticals Ireland ("Shire"). This is an important ruling that could have significant implications for companies developing orphan medicinal products.

Shire had sought annulment of an European Medicines Agency ("EMA") decision refusing to validate Shire's application for designation of its medicinal product, Idursulfase-IT, as an orphan medicinal product for the treatment of mucopolysaccharidosis, type II ("Hunter Syndrome")("the Contested Decision").

The EMA refused to validate the application because, in 2001, the European Commission adopted a decision designating "idursulfase" as an orphan medicinal product for the treatment of Hunter Syndrome ("2001 Designation Decision"). In 2007, the European Commission had then granted Shire Human Genetic Therapies AB a marketing authorization ("MA") for Elaprase, a medicine delivering idursulfase by intravenous infusion. Acknowledging this, Shire's application for orphan designation for Idursulfase-IT was based on Article 3(1)(b) of Regulation No 141/2000 ("Orphan Regulation") and the claim that Idursulfase-IT would offer significant benefit to patients affected by Hunter Syndrome compared with existing treatments, including Elaprase. In particular, Idursulfase-IT would treat the cognitive disease associated with Hunter Syndrome because it delivers its active substance, idursulfase, intrathecally, *i.e.* by injection into the spinal canal, or into the subarachnoid space, so that it reaches the cerebrospinal fluid ("CSF"). Elaprase did not do so because it did not cross the blood-brain barrier.

The EMA's refusal to validate Shire's application focused on the fact that Shire had already obtained an MA for idursulfase for the treatment of Hunter Syndrome in 2007. The application for orphan designation of Idursulfase-IT therefore did not satisfy Article 5(1) of the Orphan Regulation because it was not submitted "*at any stage of the development of the medicinal product before the application for marketing authorisation*."

The EMA also argued that the 2001 Designation Decision referred in general terms to idursulfase without specifying a particular form of administration. Accordingly, the product which is the subject of the Contested Decision, namely Idursulfase-IT, is covered by that designation and could only benefit from incentives deriving from it. In support of its position, it pointed to the

Communication from the Commission on Regulation No 141/2000 ("the Communication"), which states that "*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.*"

The European Commission intervened in the case in support of the EMA's positon.

Shire made numerous counterarguments, key to which was that the relevant provisions of the Orphan Regulation used the term "medicinal product", not "active substance." EU law makes clear that "active substance" is a different concept to "medicinal product", with the former being only one of the constituents of the latter. The EMA and Commission had confused the two concepts. Idursulfase-IT was objectively a different medicinal product to Elaprase and should be entitled to its own orphan designation.

The General Court has today dismissed all of the EMA's and Commission's arguments and annulled the Contested Decision. It has also ordered the EMA to bear its own costs, as well as those of Shire. Importantly, the General Court confirmed that where a medicinal product meets the criteria for designation as an orphan medicinal product set out in Article 3(1) of the Orphan Regulation, it may be designated an orphan medicinal product, even if that product contains the same active substance as another medicinal 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 authorized orphan product.

The General Court's findings include a number of helpful clarifications on the criteria for designation as an orphan medicinal product. These are summarized below.

1. An "active substance" is not a "medicinal product"

The Court agreed with Shire that the terms "medicinal product" and "active substance" cover two different concepts. Therefore, the fact that both Idursulfase-IT and Elaprase contain the same active substance does not necessarily mean that they are the same medicinal product.

The term "medicinal product' is defined in Article 1(2) of Directive 2001/83 as "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."

"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."

It is also established principle that a medicinal product 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."

The Court confirmed that Elaprase differs from Idursulfase-IT in its composition, method of administration and therapeutic effects. Although they contain the same active substance, Elaprase contains five excipients, while Idursulfase-IT contains only three. The two products are administered by different routes. Idursulfase-IT would allow the treatment of cognitive disorders exhibited by some patients suffering from Hunter Syndrome, which Elaprase is incapable of treating. As such, Elaprase and Idursulfase-IT are different medicinal products.

2. The holder of an MA is not restricted from applying for designation as an orphan medicinal product of a medicinal product containing the same active substance as the authorized medicine for the same indication

Neither the wording of Article 5 of the Orphan Regulation, nor the context in which that provision occurs, nor the general scheme of the Orphan Regulation, suggests that a sponsor cannot apply for designation as an orphan medicinal product of a medicinal product containing the same active substance as another product authorized in its own name for the same indication, provided it can demonstrate significant benefit over the authorized treatment.

The above position is also supported by the Communication, which further discusses the concept of "significant benefit." The Communication does not suggest that a potential medicinal product containing the same active substance as a previously authorized 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 suggests that factors such as availability of the method or ease of self-administration could show that the medicinal product is of significant benefit. Further, the Communication expressly states that "*particular benefits for a sub-sample of the population*" can provide a significant benefit. Similarly, "*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 "significant benefit" may include a more efficient formulation and means of administration than an authorized medicinal product with the same active substance and intended to treat the same condition.

3. A second, similar product may be entitled to market exclusivity

The fact that an orphan medicinal product enjoys the period of market exclusivity provided in Article 8(1) of the Orphan Regulation does not preclude a second, similar product which has been authorized pursuant to Article 8(3) of the Regulation being granted, in turn, market exclusivity, as long as it also fulfils the requirements set out in Article 3(1) of the Orphan Regulation for designation as an orphan medicinal product.

4. The verification by the EMA of the validity of an application for designation of a medicinal product as an orphan medicinal product under Article 5(4) of the Orphan Regulation is purely administrative in nature

The Orphan Regulation sets out specific, separate procedures for (1) the designation of medicinal products as orphan medicinal products, and (2) the marketing authorization of those medicinal products.

To validate an application, the EMA must first check whether the application was submitted before the application for MA (as required by Article 5(1)) and whether the application is accompanied by the information and documents referred to in Article 5(2). If the application complies with the requirements in Articles 5(1) and (2), the EMA is obliged to validate and transmit it to the Committee on Orphan Medicinal Products (COMP).

It is only at the second stage (under Articles 5(5) to (7) of the Orphan Regulation) that the COMP must adopt an opinion on the question whether the medicinal product covered by the application meets the criteria set out in Article 3(1) of the Regulation, 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 authorized.

Next steps

The judgment suggests that if Shire resubmits its application for designation of Idursulfase-IT as an orphan medicinal product for the treatment of Hunter Syndrome on the basis of Article 3(1)(b) of the Orphan Regulation, the EMA would be obliged to validate the application.

It would then be the responsibility of the COMP to assess whether the characteristics of Idursulfase-IT are likely to be of significant benefit to patients suffering from Hunter Syndrome, taking into account the relevant scientific evidence.

Subject to any appeal, the judgment also opens the possibility that companies in the orphan drug space may be eligible for separate periods of orphan exclusivity when they develop new products containing the same active substance, provided they offer a significant benefit.

If you have any questions concerning the material discussed in this client alert, please contact the following member of our Life Sciences practice:

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