King & Spalding
Client Alert

FDA and Life Sciences

OCTOBER 5, 2020

EUROPE – The General Court Limits the Scope of "Satisfactory Methods" That Must Be Compared for Orphan Drug Designation

For more information, contact:

Geneviève Michaux
+32 2 898 0202
gmichaux@kslaw.com

Christina M. Markus
+1 202 626 2926
cmarkus@kslaw.com

Cassie Rasmussen
+1 202 626 9127
crasmussen@kslaw.com

King & Spalding

Brussels
Bastion Tower
5 Place du Champ de Mars
1050 Brussels, Belgium
Tel: +32 2 898 0200

Washington, D.C.
1700 Pennsylvania Ave., NW
Suite 200
Washington, D.C. 20006
Tel: +1 202 737 0500

On 23 September 2020, in a landmark case, *Medac v Commission*, the trial-level General Court ("GC") of the European Union ("EU") annulled the decision of the European Commission ("EU Commission") that had withdrawn the orphan drug status of Trecondi (Treosulfan). The EU Commission had concluded that Medac did not demonstrate "significant benefit" of Trecondi over medicinal products containing melphalan and cyclophosphamide. The GC determined that the latter products were not "satisfactory methods" against which Trecondi had to be compared under the Orphan Regulation, because the summaries of product characteristics ("SmPC") evidenced different intended treatment conditions and populations.

This is the first time that a European Court has disagreed with the EU Commission's restrictive approach to finding a "significant benefit" in the orphan drug context. While the EU Commission will probably appeal the GC's current decision in *Medac*, the European Court of Justice should affirm the GC's decision because it accurately reflects the limits set by the Orphan Regulation, as well as its objective.

This alert briefly explains the European regime for orphan medicinal products and, in particular, the criterion of significant benefit. It then examines and comments on the case.

1. FUNDAMENTAL CONCLUSIONS OF THE *MEDAC* DECISION

The *Medac* case considers what "satisfactory methods" may be used for assessing the significant benefit that a future orphan medicinal product will bring to patients suffering from the rare condition for which an orphan designation is sought. The GC decided that:

- only "authorized" medicinal products may constitute satisfactory methods, and the scope of authorization of a medicinal product is defined in its SmPC, which is part of the marketing authorization ("MA"); and

- in light of the objective of the Orphan Regulation, authorized medicinal products that are only partly authorized for the same condition as the future medicinal product do not qualify as satisfactory methods.

This ruling clearly excludes off-label use, and also compounding, from being considered satisfactory methods, and limits the comparison for significant benefit purposes to medicinal products authorized for the same indication(s), including target populations, as the future medicinal product.

More generally, the *Medac* case illustrates the importance of the condition chosen for orphan status purposes, but also highlights the confusion around that concept. The determination of the condition is all the more important given increasing global development of orphan products and mandatory pediatric testing. Companies, therefore, should think about the condition strategically and early in the product development.

2. LEGAL BACKGROUND FOR ORPHAN MEDICINAL PRODUCTS IN THE EU

In the European Union, the legal regime for orphan medicinal products is established in Regulation 141/2000 ("Orphan Regulation")[1], elaborated by an implementing regulation and several guidelines from the EU Commission and the European Medicines Agency ("EMA").

The Orphan Regulation sets out, first, the criteria and procedure for an orphan designation ("OD") and, second, the incentives afforded in relation to the OD, in particular 10-year orphan exclusivity. In a nutshell, the OD is granted by the EU Commission following the opinion of the Committee for Orphan Medicinal Products ("COMP"), one of the scientific committees within the EMA, on whether the OD criteria are met. The OD is granted to an active substance for the treatment, prevention or diagnosis of a rare condition. The subsequent granting of an MA for a medicinal product that contains the active substance and is authorized for a therapeutic indication within the defined rare condition, automatically triggers orphan exclusivity.

The OD criteria are listed in Article 3 of the Orphan Regulation:

- a serious condition (life-threatening, chronically or seriously debilitating, or serious and chronic);
- low prevalence (less than 5 in 10,000) or insufficient return on investment; and
- "*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*". This last criterion is commonly referred to as "significant benefit".

Since adoption of the Orphan Regulation, most discussions about OD concern the significant benefit and the evidence thereof. Significant benefit is the most used criterion to justify a refusal to grant or maintain an OD. Related discussions turn around two main topics:

- ***Comparison with existing satisfactory methods***: The significant benefit must be demonstrated by comparing the future medicinal product with each satisfactory method for the condition that exists at both the EU and national levels[2]. Satisfactory methods can be surgeries, medical devices, etc. With regard to medicines, satisfactory methods are authorized medicinal products and, since the adoption of the EU Commission's Notice at the end of 2016, magistral and officinal preparations (compounding)[3]. The COMP generally requires direct comparative data but accepts indirect comparative data under certain circumstances. The main issue of discussion is the regulators' very broad discretion: about what constitutes a "satisfactory method", about the relevant condition, and about the evidence value of comparative data brought by the company.
- ***Maintenance of the OD***: The EU Commission has interpreted the Orphan Regulation as requiring a company to prove that the OD criteria are met, not only at the time of granting the OD, but also at the time of granting the MA. Typically, companies apply for an OD early in their development program. This is especially true of small- and medium-sized companies because an OD is a positive sign that triggers third-party investment. At that time, however, the company typically does not hold enough data to demonstrate scientifically the significant benefit of its future medicinal product. The COMP, therefore, accepts a significant benefit based on preliminary data and assumptions. Following the COMP's positive opinion, the EU Commission grants the OD. Then, the company develops its product and collects scientific data to support the MA application. When the company files its MA application, it must submit

an "orphan maintenance report" to demonstrate that its medicinal product indeed brings a significant benefit when compared to existing satisfactory methods and thus the OD may be maintained. At this point in the process, the COMP only accepts the significant benefit based on scientific data. In addition, the COMP only examines the OD criteria after the EMA's scientific assessment because the assessment determines the therapeutic indication of the future medicinal product, and that indication is the measure for the significant benefit. If the COMP gives a negative opinion, the EU Commission withdraws the OD right before granting the MA.

Arguably, this two-step approach makes sense because, in practice, companies are unable to bring the scientific evidence of a significant benefit at the initial time of granting the OD.

Yet, this approach defeats the very purpose of the Orphan Regulation. If the EU Commission withdraws the OD before granting the MA, the medicinal product does not have orphan status and, thus, is not protected by orphan exclusivity. In other words, the company invested in the development of an orphan product believing that it would benefit from orphan exclusivity and be able to recoup its investment; however, that incentive disappears after the investment is made.[4] This risk is not one that all companies and investors are willing to take, especially in the case of old active substances. Accordingly, first, this approach undercuts the objective of incentivizing the development of products for rare diseases.

Second, the two-step approach requires companies to submit comparative data in relation to the satisfactory methods existing at the time of granting the MA, i.e., in relation to medicinal products authorized between the granting of the OD and the granting of the MA. This may prove very challenging when either (i) the development of the orphan product took many years so that several new medicinal products have been authorized for the condition since the granting of the OD; or (ii) the new comparative products have only been authorized very recently so that very little data has been published thereon[5].

Over the last years, the EU Commission and the COMP have become more restrictive regarding the concept of significant benefit and more demanding regarding the evidence of significant benefit, which has resulted in more OD not being maintained or being "voluntarily" withdrawn by companies.

3. COURT RULING IN THE *MEDAC* CASE (T-549/19)

Facts. – On 23 February 2004, the European Commission granted Medac an OD for Treosulfan (active substance) for "conditioning treatment prior to haematopoietic progenitor cell transplantation" (rare condition).

On 13 October 2017, at the time of MA, Medac submitted an orphan maintenance report.

On 19 December 2018, the COMP adopted an opinion on the maintenance of the OD for Treosulfan and concluded that Medac did not demonstrate significant benefit in comparison with medicinal products containing melphalan and cyclophosphamide (because the indirect, literature-based comparisons provided by Medac were insufficient to substantiate a clinically relevant advantage of Trecondi). Medac requested a re-examination of the opinion and submitted new analyses comparing Trecondi with melphalan- and cyclophosphamide-based products. The COMP, however, confirmed its initial opinion.

On June 20, 2019, the EU Commission granted an MA for Trecondi but decided not to classify this medicinal product as an orphan medicinal product and withdrew the OD for Treosulfan.

Medac filed an application for annulment of the EU Commission's decision on the OD.

Court Decision. – In essence, Medac claimed that medicinal products containing melphalan and cyclophosphamide were not "satisfactory methods" for the condition treated by Trecondi (and therefore should not be used to judge significant benefit). Five main arguments were raised, but the General Court only examined the first two arguments, as it concluded that they had merits.

The first two arguments simply alleged wrongful interpretation of the concept of "satisfactory method" under Article 3 of the Orphan Regulation and the 2016 Commission Notice. The General Court ruled in Medac's favor on the following grounds:

- A medicinal product may only be classified as a "satisfactory method" if it is "authorised" in the EU or in a Member State for the same orphan "condition" as the condition covered by the future medicinal product.

- The scope of the authorization of a medicinal product is defined in the decision granting the MA, of which the (updated) SmPC forms part. Therefore, the off-label use of a medicinal product cannot be regarded as being "authorised" and a medicinal product used off-label cannot constitute a "satisfactory method".

- All the essential elements surrounding the authorized use of an existing method and, in particular, its therapeutic indication and target population as defined in its SmPC, must be taken into account to determine whether an existing method covers the same "condition" as that covered by the future orphan medicinal product. And SmPCs must be interpreted strictly.

- Where the future medicinal product is intended for the diagnosis, prevention or treatment of conditions or categories of patients for which comparative medicinal products are not authorized according to their respective SmPCs, those latter medicinal products cannot be regarded as being "satisfactory methods".

  The exclusion of a potential medicinal product from the benefits of the Orphan Regulation on the ground that "satisfactory methods" exist only for a portion of the rare conditions covered by the future medicinal product is contrary to the intended purpose of the Orphan Regulation.

- It thus is appropriate to examine whether the treatment of the orphan condition and the categories of patients targeted by Trecondi are also covered by melphalan- and cyclophosphamide-based medicinal products, according to their respective SmPCs.

- The SmPCs of the medicinal products to be compared show clear differences. The SmPC of Trecondi covers pathological conditions and populations which are not covered by the SmPCs of melphalan- and cyclophosphamide-based medicinal products so that those products cannot be regarded as satisfactory methods. There is a partial overlap between the conditions and the populations covered by the medicinal products, but it remains that Trecondi is indicated for conditioning treatment prior to an allogeneic HSC transplantation in the case of certain pathological conditions and certain categories of patients for which melphalan- and cyclophosphamide-based medicinal products are not indicated.

4. COMMENTS

Concept of "satisfactory methods". – The *Medac* ruling is important because:

- it establishes that only "authorised" medicinal products may constitute satisfactory methods for comparison and then expressly ties the authorization to a MA and excludes off-label use. Importantly, this also should exclude magistral and officinal preparations that the EU Commission has considered as satisfactory methods since the end of 2016; however, the latter products were not expressly addressed by the *Medac* decision.
- it decides that only the medicinal products authorized for the same indication(s) as the future medicinal product constitute satisfactory methods with which the future medicinal product should be compared. This ruling puts the objective of the Orphan Regulation back into the assessment of the OD criteria. As the GC rightly stated: potential orphan medicinal products may not be denied the benefits of the Orphan Regulation on the ground that "satisfactory methods" exist only for a portion of the rare condition covered by the future medicinal product. Moreover, insofar as the label of a future medicinal product is broader than those of previously authorized medicinal products for the condition, the future medicinal product undoubtedly does bring a significant benefit to patients who are affected by the rare condition, be it to only part of them. Requiring a comparison therefore is unnecessary.

Concept of "condition". – *The Medac* case illustrates the importance of the condition chosen for orphan status purposes, but also the confusion around that concept.

- The term "condition" is not defined in the Orphan Regulation. However, the 2016 EU Commission Notice and the Commission's Guideline on Orphan Designation[6] define a condition as "*[…] any deviation from the normal structure, or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised disease or a syndrome).*" This term is used instead of "disease" in order to cover non-classical diseases such as genetic disorders.

  The Guideline on Orphan Designation specifies that, when applicable, companies should refer to the condition according to "*International disease classification systems such as the WHO's International Classification System (ICD) or other well recognised systems*". The WHO ICD classifies diseases based on symptoms and thus is a medical/clinical classification of diseases. The next version of the WHO ICD – ICD 11, which will enter into force in 2022 – contains a definition of "disease": "[… *a set of dysfunction(s) in any of the body systems defined by: 1. symptomatology - manifestations: known pattern of signs, symptoms and related findings, 2. etiology: an underlying explanatory mechanism, 3. course and outcome: a distinct pattern of development over time, 4. treatment response: a known pattern of response to interventions, 5. linkage to genetic factors: e.g., genotypes, patterns of gene expression, 6. linkage to interacting environmental factors.*"

- In the *Medac* case, the condition was "conditioning treatment prior to haematopoietic progenitor cell transplantation".

  Haematopoietic progenitor (or stem) cell transplantation (HSCT) is a procedure that infuses (autologous or allogenic) stem cells to re-establish haematopoietic function in patients with damaged or defective bone marrow or immune system. Before certain HSCT, cells that may react against the stem cells have to be eliminated – this is a conditioning treatment prior to HSCT.

  In its orphan maintenance assessment report of 20 June 2019, the COMP indicated that (i) it recognizes HSCT as a treatment modality for the delineation of an orphan condition, which is only used in exceptional cases; (ii) in light of this exception, the initial orphan indication "Conditioning treatment prior to [HSCT]" remains acceptable; and (iii) now and for future OD, the COMP generally designates the slightly reworded orphan condition "treatment in HSCT". The COMP refers to the Guideline on Orphan Designation according to which "*[e]xceptionally, a particular treatment modality could be considered to define a distinct condition. This could apply to products needed in medicinal procedures, but regardless of the specific underlying condition*."

  HSCT is a rare (0,67 in 10,000) and serious (risk of severe infections and of graft vs host disease) procedure designed to treat conditions, some of which are rare but it is not a condition. Granting an OD for a procedure is questionable under the Orphan Regulation that expressly refers to "condition". Logically, the OD should be granted for each condition to be treated by the HSCT since the future medicinal product will treat those conditions, be it indirectly. Regulators however disfavor this approach because it would lead to many more OD.

  Granting an OD for a procedure also raises practical issues when applying the OD criteria and, in particular, identifying the satisfactory methods as the *Medac* case illustrates. One may also wonder about orphan exclusivity. Does the OD for treatment of HSCT prevent, for the same active substance, a second OD for one of the conditions that could be treated by HSCT?

  Yet, such interpretation may be necessary for the orphan regime to support the scientific and technological development in life sciences. Indeed, a search on the EMA website shows that, since 2016, more than 10 OD have been granted for "treatment in HSCT", mainly to biological substances to be used in cell and gene therapy medicinal products.

- The concept of condition is also central to the application of the Paediatric Regulation, and a definition of "condition" is included in the EU Commission's Guideline on Paediatric Investigation Plans[7] ("PIP") that is the same as that used in the rare diseases context. However, the approaches to the condition are different:
  - In the pediatric area, the EMA generally relies on the Medical Dictionary for Regulatory Activities (MedDRA) rather than on the WHO ICD, because the former broadens the EMA's choice of the relevant

condition/disease for the PIP. (MedDRA, however, classifies diseases and conditions based on safety incidents and thus is less suited than the WHO ICD for the purposes of the Paediatric Regulation.)

- Moreover, while the COMP tends to use broad conditions to reduce the number of OD, the Paediatric Committee (PDCO) tends to use narrow conditions to reduce the scope of the PIP and thereby secure more PIPs for the same active substance. These opposite approaches create tensions for pediatric orphan medicinal products.

Given the overlap between orphan and pediatric conditions/diseases, it is key to align the two legal regimes with regard to the determination of the relevant condition.

- Development of orphan products is global, and the EMA and U.S. Food and Drug Administration ("FDA") cooperate closely in the orphan area (as well as in the pediatric area). The EU and U.S. criteria for OD are different. Under the U.S. regime, the prevalence is lower (200,000 vs 5 over 10,000, i.e. 255,000 currently in the EU) and, more importantly, generally no judgment of significant benefit is required.

  Yet, comparable definitions and references should be used in the EU and the U.S. in order to support the granting of OD for the same conditions and thereby global development of orphan drugs.

  Like the EMA, FDA has granted more than a dozen OD for treatment of patients receiving HSCT and several OD for "conditioning treatment prior to hematopoietic progenitor cell transplantation". Interestingly, with regard to Treosulfan, FDA also granted an OD for "conditioning treatment prior to haematopoietic progenitor cell transplantation" but added "in malignant and non-malignant diseases in adult and pediatric patients". Moreover, the most of the OD granted in relation to HSCT, are for "enhancement of cell engraftment…" or "prevent of morbidity and mortality…" associated to HSCT.

Joint Evaluation of the Paediatric and Orphan Regulation. – The recent EU Commission's Joint Evaluation of the Paediatric and Orphan Regulations ("Joint Evaluation") (see previous alert) does not discuss the issue of significant benefit and does not suggest any legislative or other modification to the current system. Yet, this is the most disputed aspect of the Orphan Regulation by the pharmaceutical industry as shown, inter alia, by the number of cases before the European Courts of Justice. On the other hand, the Joint Evaluation clearly indicates that the basic concepts have to be redefined for purposes of both the Orphan Regulation and the Paediatric Regulation, and those basic concepts include "condition".

5. KEY MESSAGE

The *Medac* ruling provides arguments for companies to oppose the choice of "satisfactory methods" imposed by the COMP and reduce the comparisons mandated with their future orphan medicinal products.

It also shows the importance of the "condition" at issue for future orphan medicinal products. Choosing the condition is a strategy exercise because that choice will impact the "satisfactory methods" and, thus, the orphan status, orphan exclusivity, and pediatric development.

Coming out of this decision, companies should define the condition in light of the COMP's current practice, but also keep in mind both the future adult and pediatric development and, of course, global development (i.e. the approaches adopted by FDA and other regulators). In practice, companies should identify the "best" condition, develop scientific arguments to justify their choice, identify the "satisfactory methods" of that condition, and then request scientific advice for significant benefit so that they can discuss and confirm their choice and selection in advance with the EMA and other regulators.

King & Spalding is regularly working with companies to help make the best decisions early on in the process to ease the path for orphan medicinal products.

ABOUT KING & SPALDING

Celebrating more than 130 years of service, King & Spalding is an international law firm that represents a broad array of clients, including half of the Fortune Global 100, with 1,200 lawyers in 22 offices in the United States, Europe, the Middle East and Asia. The firm has handled matters in over 160 countries on six continents and is consistently recognized for the results it obtains, uncompromising commitment to quality, and dedication to understanding the business and culture of its clients.

ABU DHABI	CHARLOTTE	GENEVA	MOSCOW	RIYADH	TOKYO
ATLANTA	CHICAGO	HOUSTON	NEW YORK	SAN FRANCISCO	WASHINGTON, D.C.
AUSTIN	DUBAI	LONDON	NORTHERN VIRGINIA	SILICON VALLEY	
BRUSSELS	FRANKFURT	LOS ANGELES	PARIS	SINGAPORE	

[1] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.
[2] GC, 16 May 2019, *GMP-Orphan v Commission*, T-733/17 and ECJ, 11 June 2020, C-575/19 P.
[3] EU Commission Notice of 18 November 2016 on the application of Articles 3, 5 and 7 of Regulation No 141/2000. See G. Michaux and L. Salernitano, *How drug preparations undermine Europe's regulatory system*, Scrip. 30 Nov. 2018.
[4] On this issue, see G. Michaux, *Demonstrating significant benefit for orphan medicines – is it time for a drastic change*, Scrip. 8 June 2016.
[5] GC, 5 Dec. 2018, *BMS v Commission*, T-329/16.
[6] EU Commission, Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another, 27 March 2014.
[7] EU Commission, Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies, 27 Sept. 2014.