EU Orphan Drug Designation – overcoming regulatory challenges

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The regulatory environment

Since the introduction of the EU orphan legislation in 2000, treatments for rare diseases now account for approximately 25% of all marketing authorization applications in the EU (EMA annual report, 2020). Clearly, the incentives offered by the ODD process have encouraged sponsors to pursue innovations in this domain. Yet while orphan status has been granted to more than 2,300 medicines, only 192 have received marketing authorization. There is no question that success or failure depends on multiple factors. But sponsors can amplify their prospects for gaining authorization by better understanding the regulatory considerations involved in bringing their innovations to patients awaiting them.

Applying for ODD

To take advantage of these incentives, sponsors must first submit an application for ODD to the committee for orphan medicinal products (COMP). While the criteria might appear straightforward, our experience is that many underestimate the requisite burden of proof and justification. For ODDs submitted according to the 'prevalence' category, these requirements include the following:

About the author

Dr. John McIntyre supports Parexel's clients in successfully navigating the EU orphan drug designation (ODD) process. With over 15 years of experience in the pharmaceutical industry, he is passionate about helping clients bring innovative therapies to market to overcome the struggles patients, and their families face every day. In this article, John shares his expertise, looking at common pitfalls with ODD and highlighting strategies to overcome them. He also outlines several regulatory precedents and landmark legal cases that sponsors should consider when formulating regulatory strategies around orphan development.

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- The condition must be **'life-threatening or chronically debilitating'** (Regulation EC 141/2000, Article 3(1) a). While in some cases, the sponsor can point to reduced life expectancy or otherwise obvious significant effect on the quality of life or associated morbidity, more 'borderline' conditions could exist that are less clear-cut. Recent examples include COMP's opinion on fibromyalgia (COMP, 2019).
- The condition must meet the **prevalence requirements** of affecting no more than five persons per 10,000 of the population in the EU (Regulation EC 141/2000, Article 3(1) a). Here, the guidance asks for a review of the literature and any reference databases, together with a critical presentation of methods, results, and conclusions (COMP guidelines, 2019). Therefore, sponsors may not rely on ODD approval in a given condition to preclude them from performing such a prevalence assessment.

  The COMP's logic rests on the fact that prevalence is a variable that may change due to increased disease incidence or improvements in disease diagnosis or management. Sponsors should be aware of the sometimes complex nature of such assessments – for example, estimating prevalence from incidence and disease duration and when to use complete or partial prevalence calculations. Moreover, the published literature may inaccurately report 'prevalence' or 'incidence,' and the underlying approach and interpretation of definitions may be erroneous.
- **'Significant benefit.'** The sponsor needs to ensure that there is no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the European Community. If such a method exists, the proposed medicinal product is likely to be of significant benefit to those affected by that condition (Regulation EC 141/2000, Article 3(1) b).

  This 'significant benefit' argument is perhaps one of the most challenging aspects of the ODD application process because sponsors must perform a comparative exercise with approved medications in the indication. A significant benefit could be based on improved efficacy, improved

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safety, or a major contribution to patient care, such as a formulation associated with better compliance or improved quality of life.

This aspect of the ODD has increasingly been required to rely on data demonstrating the specific benefit compared to the authorized medicine, and the burden of proof is getting higher. This argument is typically based on improved efficacy and should be supported by non-clinical and, if possible, clinical data. For example, this might center around an aspect of the disease addressed by the candidate orphan drug that is not addressed in the label of the authorized medicine. (The concept of 'clinical superiority' is defined in Regulation EC 847/2000.) Given that many applicants might not have direct comparative data, methods for indirect comparison may be used in some situations. However, such comparisons should be interpreted cautiously due to potential differences in patient population, trial methodology, and other important factors.

- A critical but often overlooked aspect of the ODD application process is the **choice of orphan** indication itself. The orphan indication could be broader than the proposed therapeutic indication and must be a 'distinct medical entity.' Such entities must be distinguished in their specific characteristics, including pathophysiology, histology, clinical characteristics, or etiology.

  The concept of a 'distinct medical entity' (as opposed to a subset of a rare condition, such as a particular disease severity) is important. It ensures that the spirit of the orphan legislation is kept intact: that incentivization is limited to rare diseases. However, the guidance does exceptionally consider subsets of non-rare conditions if the subset presents distinct evaluable characteristics with a plausible link to the condition, and if they are essential for the medicinal product to carry out its action.

  An example exemption could be based on genetic characteristics associated with the subset. This would be the case if characteristics are closely linked to the medicinal product's pharmacological action, and the absence of the characteristics will render the product ineffective in the remaining disease population. It is also worth noting that COMP has granted orphan designations outside of this strict 'distinct medical entity' criteria, including disease symptoms, subsetting based on severity/stages or biomarkers, and treatment modalities (reviewed in O'Connor et al., 2019).

- Finally, the concept of **'medical plausibility'** requires sponsors to provide evidence that the candidate drug is likely to have a relevant effect in the orphan condition application. Since many sponsors may be at early-stage development with only pre-clinical data available, this can present challenges, although COMP does accept only pre-clinical data for orphan applications.

  Sponsors should aim to frame their results in the context of the orphan indication applied for and include discussion on the validity of animal models of disease. However, even in small numbers of patients, additional clinical data increases the chance of a successful grant of orphan designation. Clinical data should also be relevant to the sought orphan indication in terms of the study population, clinically relevant endpoints and outcomes, and study design considerations.

Legal precedents

Recent legal cases have illustrated the importance of understanding the nuanced regulatory considerations relative to market exclusivity when developing orphan medicines or a generic version of an orphan. Market exclusivity has been extended through product improvement or reformulation in some situations, and the companies' first past the post' bear advantages over subsequent entrants.

One case involved a product granted orphan designation that gained marketing authorization (MA) for ten years of exclusivity under Article 8 of Regulation No 141/2000. After the expiration, the sponsor applied and gained ODD status and MA for a similar compound in related indications. The EMA granted exclusivity in this case because, although the product was deemed a 'similar medicinal product' under Article 8 (1), the application addressed Article 3 (1)(b) of the orphan regulation (significant benefit).

The sponsor was able to apply the derogation of 'consent' provided for in Article 8(3)(a), permitting the marketing of the second product. The second ODD grant prevented the entry of generics to the original compound when the 10-year period of market exclusivity lapsed (Case C-138/15 P). This case demonstrates the importance of Article 8(3)(a), where a sponsor can gain approval to market an 'improver' molecule that precludes generic development of either the original or improver molecule for ten years.

A second case involved a sponsor that was granted orphan designation and marketing authorization to formulate an enzyme for intravenous infusion to treat manifestations of a disease affecting the central nervous system. The sponsor subsequently developed an intrathecal (IT) formulation of the compound to cross the blood-brain barrier.

There were differing perspectives among regulatory authorities regarding a second orphan designation. The question pertained to compliance with Article 5(1) of Regulation No 141/2000, which specifies that an application for designation must be made before granting marketing authorization. Further, the original ODD decision was thought to refer in general terms to the enzyme without specifying a particular form of administration.

The prevailing reasoning was based primarily on the interpretation that 'medicinal product' and 'active substance' cover two different concepts. The initial IV formulation of the compound was eventually deemed a medicinal product different from the IT formulation, allowing for granting of orphan status for the IT formulation (Case T-80/16).

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Background on the ODD Regulation

The EU orphan drug regulation (Regulation EC 141/2000) was introduced in 2000 to encourage the development of so-called 'orphan' medicines, offering several key incentives to foster commercial viability. Specifically, the orphan drug designation (ODD) supports the development of medicines intended to diagnose, prevent, or treat life-threatening or chronically debilitating conditions affecting not more than five in 10 thousand persons in the European Union.

ODD offers both pre-marketing and post-marketing incentives:

- Pre-marketing incentives include fee reductions for regulatory procedures such as protocol assistance, as well as access to the centralized procedure facilitating EU-wide marketing authorization.
- Post-marketing incentives include fee reductions for regulatory procedures and market exclusivity for a 10-year period.

To take advantage of these incentives, sponsors must first submit an application for ODD to the committee for orphan medicinal products (COMP), which will adjudicate on the submitted data. A sponsor can choose from two routes to apply for orphan designation for their medicinal product:

- 'Prevalence': The prevalence of the condition in the EU is not more than five in 10,000.
- 'Return on investment': It is unlikely that marketing the medicinal product in the EU, without incentives, would generate sufficient return to justify the necessary investment.

For the latter, Regulation EC 847/2000 outlines the necessary information required to make the assessment. This includes:

- Details of past and future costs associated with the development of the product
- Estimated sales revenue in the first ten years following authorization
- Details of grants, tax incentives, or other cost recovery provisions received
- Past and future production and marketing costs

Note that this category accounts for less than 1% of orphan medicinal product designation applications.

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- Review, critique, and gap analysis of your data package or draft submission from a regulatory perspective

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