

Increasing Pressure on Orphan Medicinal Product Designations in the EU

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Food, Drugs, and Devices

In the EU, a sponsor can obtain an “orphan designation” for a medicinal product pursuant to Regulation 141/2000. Adopted in December 1999, the regime aims to encourage investment in R&D for treatments for rare diseases. The most important incentive is the 10-year market exclusivity for designated products. Other incentives include protocol assistance and fee reductions. At the national level, there may be benefits under pricing and reimbursement procedures and, for instance, also tax incentives.

The EU orphan medicines regime is a success. By early 2016, the European Commission had granted more than 1,500 orphan designations and more than 100 marketing authorizations covered orphan indications. However, the success has led to a backlash. Strong political pressure has emerged, criticizing the EU orphan exclusivity rules because of a perceived impact on drug pricing and healthcare budgets. There have also been allegations of “sub-setting” rare conditions to increase the opportunities for additional periods of market exclusivity.

These political pressures are resulting in an increasingly restrictive approach to the granting, maintenance and review of orphan designations in the EU. In this note, we highlight the three main instances where designation can be challenged:

1. the initial granting of the orphan designation;
2. the maintenance of the designation at the time of the marketing authorization; and,
3. the review of the orphan designation after the marketing authorization has been granted.

Granting Orphan Designation

Applications for an orphan designation must always be submitted before the marketing authorization application. The sponsor must identify the active ingredient, the proposed therapeutic indication, and provide a justification for the orphan designation. As justification, the sponsor will typically show (i) that the condition does not affect more than 5 in 10,000 persons in the EU (the “prevalence criterion”), and (ii) either that there is no satisfactory method of treating the condition, or that the medicinal product will be of significant benefit compared to existing authorized medicines or other treatment methods (“significant benefit criterion”).

Applications are submitted to the European Medicines Agency (“EMA”), which checks the dossier and “validates” the application when it is complete and, in principle, admissible. Recent experience shows that this first step in the procedure has become more challenging. A refusal to validate is currently pending before the EU Court in *Shire v EMA* (Case T-

80/16), where the EMA refused to accept an application for an orphan designation because it considered that the conditions for designation were not (or could not be) established. The validation step can thus already go into the substantive designation criteria.

The second hurdle is of course the granting process itself. The conditions for granting an orphan designation are now also more strictly scrutinized. For example, when looking at the prevalence criterion, the EMA's Committee for Orphan Medicinal Products ("COMP") will thoroughly examine and challenge the sponsor's methodology to calculate the population that is "affected by" the condition. For illnesses where patients live longer, for instance, due to improvements in treatment, this can have a real impact. If the COMP challenges certain methodological choices in the prevalence calculation, this can put the sponsor "under or over" the prevalence threshold. For significant benefit, assumptions may be used, but they will have to be confirmed at the maintenance phase.

Review of Orphan Designation at the Time of Marketing Authorization

At the time of marketing authorization, the COMP will review whether the orphan designation criteria are still met. This is the so-called "maintenance review." In the past, this review was typically not very demanding, but in part due to the increased number of approved orphan medicines, the EMA and the Commission now take a much stricter approach to the maintenance review. The COMP will address all the criteria for the designation, including the seriousness of the condition and its prevalence. We provide two examples.

First, the EMA and the Commission consider that the prevalence must also be reviewed again as of the time of the maintenance decision. This interpretation contradicts language of EU Regulation 141/2000 that only refers to prevalence at the time of application for the initial designation. Nevertheless, sponsors are expected to provide data indicating that the population affected by the condition remains at less than 5 in 10,000.

Second, sponsors must also provide additional data proving the original assumption of significant benefit of the medicine over existing authorized therapies. In assessing this, the EMA will even take into account recently approved medicines. This can include, for example, a product that has received marketing authorization less than two months before the COMP conducts the maintenance review. This is one of the issues at stake in the pending litigation before the EU Court in *BMS v Commission and EMA* (Case T-329/16). A decision is expected later this year and may have an important impact on how the maintenance review is conducted. The legal questions relate to the procedure to be followed by the Commission when withdrawing the designation before the marketing authorization is granted, and, more importantly, the grounds for withdrawal. Among others, the Court may clarify whether the designation should be maintained when the available data do not allow a clear conclusion on significant benefit over a new product.

Review of Orphan Designation after the Marketing Authorization

Once a medicinal product with an orphan designation is granted a marketing authorization, it will automatically benefit from market exclusivity for a period of 10 years. At that point, the orphan designation can still be reviewed in two cases.

First, the EU Regulation allows to reduce the market exclusivity from 10 to 6 years, if after 5 years it appears that the designation criteria are not met any more. The Regulation adds that this may be the case when the product is sufficiently profitable. There is only one public example of an attempt to do so and the exclusivity was maintained at 10 years. However, in

October 2017, the COMP chairperson stated that given the increasing number of orphan medicinal products coming on the market, there is a need to “fully exploit the legal possibilities” to reduce protection periods for orphan medicines “that do not meet the criteria over time.” According to him this “entails the need to generate relevant data for these products after authorization.”

Second, the Commission Notice of November 2016 explicitly allows a further review in case of a major variation of the marketing authorization, such as extending the therapeutic indication within the scope of the existing orphan designation. This review of the orphan designation at the time of a variation is new, and was not applied in the past. As a result, the sponsor may be asked to once again substantiate the fulfilment of the designation criteria, “if the specific scope of the variation raises justified and serious doubts in this respect.”

Finally, we highlight that the European Commission is currently also reviewing the “similarity” criterion.” Under the EU orphan medicines Regulation, market exclusivity implies that no marketing authorization will be granted for the same therapeutic indication, in respect of a “similar” medicinal product. A public consultation on this topic finished at the end of November 2017. “Similarity” is an important element of the orphan medicines regime. Broader similarity blocks more competitors, while more narrow similarity decreases the incentive value of an orphan designation.

Practical Recommendations

Due also to political pressure, the EMA and the Commission are pursuing a stricter interpretation and application of the procedures to grant, maintain, and review orphan designations. Pharmaceutical companies should prepare for these changes, especially since the deadlines for the review of designation can be strict and it is often time consuming to compile the relevant data.

Some practical recommendations are:

- Have procedures in place for regular updating information supporting the key designation criteria. This in particular includes prevalence, status of other approved products (and methods) and comparative data on significant benefit.
- For products going through the initial marketing authorization procedure or for which a new indication is applied for, carefully map the approved alternative products, including changes in the therapeutic indications, as well as expected new approvals.
 - The same should be done for approved orphan medicines during the fifth year following the marketing authorization.
- Verify whether there are clear therapeutic alternatives available as magistral or officinal preparations.
- Update prevalence calculations based on a sufficiently long survival period.
- Explore possibilities to provide data to support significant benefit, based on direct or, if needed, indirect comparisons and providing quantitative assessments.
- Map therapeutic guidelines and treatment recommendations in the specific therapeutic area.

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