How to Successfully Navigate Orphan Drug Designation

Author

Terese Johansson MSc, PhD
Senior Regulatory Strategy Manager
Global Regulatory Affairs
PRA Health Sciences
Introduction

Obtaining Orphan Drug Designation (ODD) is an essential step that significantly strengthens the business case and investment basis for early stage drugs, often providing the needed momentum to enter the clinic. Taking advantage of early regulatory tools and designation programs, such as obtaining an ODD, is often reflected in increased stock prices for pharmaceutical companies and can, for early development companies, provide important signals to investors that the drug may have financial value (1-3).

The past decade has seen more rare disease (orphan) drug development and approvals than ever with European Medicines Agency (EMA) and the Food and Drug Administration (FDA) receiving record-breaking numbers for applications year on year. For companies developing orphan drugs, this also means increased barriers when it comes to showing proof of medical plausibility, clinically superiority, significant benefit over existing therapies, and prevalence of the disease. Having a strong regulatory and scientific strategy significantly improves the chance of success for an orphan designation, and saves valuable time and money.

The timing for applying for orphan designation should be carefully determined. An orphan designation may in addition to the potential stock increase add value to a product by enabling promising press releases, increasing the company visibility, and it is a way to initiate early interactions with Health Authorities. However, seeking an orphan designation too early has its disadvantages, including public disclosure of regulatory strategy, product positioning, and risking a premature application with a following rejection due to insufficient data. As a result, when to submit an ODD is subject to particular consideration.

Qualifying Criteria and Incentives for Orphan Drug Designation

The qualifying criteria for obtaining an ODD differ depending on geographical region, and so do the incentives that comes with it. A common mistake, easily made, is believing that a drug is an orphan product before it obtains ODD.

The 1983 Orphan Drug Act was established by the US FDA to facilitate the development of drugs targeting orphan diseases, defined as diseases that affect fewer than 200,000 people at any given time or drugs that would not likely generate sufficient return to justify the investment needed for its development in the US market (return on investment criterion). Companies must demonstrate that there is “promise” that the drug will be effective in treating the disease and that it is clinically superior to other similar drugs that have received ODD for the indication. Drugs with ODD are eligible for grants, 50 percent tax credit for expenditures incurred during the clinical testing phase, and a seven-year marketing exclusivity period.

In 2000, the EU adopted the Orphan Regulation (EC No. 141/2000). EU companies must show that the drug should be intended to prevent, diagnose, or treat a life-threatening or chronically debilitating disease. In addition, the condition may not affect more than 5 in 10,000 people or individuals, or that without incentives, it is unlikely that the marketing of the medicinal product in the community would generate sufficient return to justify the necessary investment (= return on investment criterion). Satisfactory methods of diagnosis, prevention, or treatment should not exist/are not authorised or, if a medicine exists, the orphan drug being studied must demonstrate significant benefit over the existing one. Sponsors who obtain ODD benefit from protocol assistance (a type of scientific advice specific for designated orphan medicines), ten years market exclusivity once the medicine is on the market. It can be reduced if the orphan criteria(s) is no longer met, and fee reductions are available depending on the status of the sponsor and the type of service required.

Rarity is the key concept on which the orphan diseases definition rests, either in terms of absolute numbers of patients in the US, or in rates of prevalence in EU (or other regions). For calculations of prevalence, the specific epidemiological measure for disease frequency should be specified and justified and for any indirect calculations. All assumptions need to be justified by referring to scientific literature. Establishing the true prevalence (the proportion of diseased individuals, whether diagnosed or not, in a population at a given time) of a rare disease can be particularly challenging. Since epidemiological reports are often scarce, they may not be standardised or can be difficult to combine.

One method of estimating prevalence is to extrapolate from current incidence data—an epidemiological measure of the rate of new occurrence. However, the methodological challenges in counting small populations and factors such as changes over time in disease definition and diagnostic criteria may impact prevalence calculations and should be taken into account.

For certain rare haematological malignancies like Chronic Lymphocytic Lymphoma and Multiple Myeloma/Plasma Cell Myeloma, the new available treatment options providing better outcomes have increased the overall survival rates for the patients, leading to larger patient populations and increasing prevalence rates (4). For these diseases, and other conditions like them, the criteria’s proposed for prevalence calculations should be carefully considered (ie, partial- or point prevalence). Partial prevalence estimates are reported over a limited period of time, such as 5-year or 10-year prevalence (capturing all living patients who had been diagnosed cases in the timespan of the preceding 5 or 10 years) whereas point prevalence is the proportion of a population that has the condition at a specific point in time irrespective of the time of diagnosis.

Diseases may be rare in a specific geographical area (ie, Western Europe) whereas it is not rare in another. A typical example of this are infectious diseases, like certain types of tuberculosis and malaria. Population migrations will also influence the incidence and prevalence of diseases. For example, nowadays, a haemoglobinopathy typical for African-like sickle cell anemia is becoming more frequent throughout Europe.

The Orphan Condition, Sub-Setting of Common Conditions, Natural History Studies, and Biomarkers

The definition of an acceptable orphan condition is an essential starting point for the assessment of any ODD application. Regulators look at orphan diseases in broad terms, avoiding designations relating to artificial subsets of a particular condition (ie, so-called sub-setting of common diseases). Sub-setting a condition is not acceptable unless it is possible to provide solid evidence that the activity of the product cannot be shown on the larger patient population, ie, the applicant needs to demonstrate that the drug does not work outside the subset. Furthermore, symptoms of an underlying disease will most likely not qualify for orphan designation. A designation may be granted if sponsors can “support the designation with robust evidence demonstrating the pivotal role of the symptom in the condition and its clinical impact” (5).

For orphan diseases, the FDA recommends natural history studies (epidemiological studies that focus on describing the frequency, features, and evolution of a disease by collecting real-world data from groups of patients suffering from this disease) to better characterize patient populations and delineate target populations (6). For diseases with substantial heterogeneity in clinical presentation, improved predictive ability based on the natural history of the disease may inform inclusion/exclusion criteria to facilitate an effective clinical trial program, and help to identify potential biomarkers to guide treatment (7, 8).

In the US, the FDA has granted ODDs for so-called tissue agnostic cancer treatments based on the presence of a specific biomarker (9, 10). In the EU, biomarkers have been used in marketing authorization submissions to further support and define an orphan condition and to justify that the criteria for
Medical Plausibility, Relevant Disease Models, and Preclinical Data for Products in Early Development

In the EU, the concept “medical plausibility” refers to the “intention to diagnose, prevent, or treat” the orphan condition. When an orphan designation is sought, often early, during the development, it is common that little to no clinical experience is available. As a result, it’s important that the preclinical studies use relevant models and endpoints. The models should replicate the features of the medical condition as closely as possible to allow for extrapolations to be made and to draw conclusions for the condition. Early preclinical studies, such as in vitro studies alone, are often not enough to gain regulatory approval, since they are more difficult to interpret than higher level studies performed in validated animal models of disease. As a general rule, to support designation, at least relevant in vitro and in vivo data in appropriate preclinical models should be submitted (14). The endpoints chosen in the preclinical studies should be relevant to the clinical target sought, thereby aiding regulators to make a meaningful assessment of relevant improvements secondary to the pharmacological intervention. If clinical data is available at the time designation is sought, the preclinical data should be discussed in full, even if preliminary results from first administration to humans are available. EU numbers indicate that 30% of the designations are approved based only on non-clinical data (in a relevant model) REF!, the figure for US is unknown. For some conditions, EU regulators have published papers addressing what is considered to be a relevant animal model(s) (15-17).

Bridging data from other products, irrespectively of how comparable they may be, or from settings not directly associated with the condition, is only exceptionally considered useful.

Clinical Superiority (US) vs Significant Benefit (EU)

The Clinical Superiority concept in the US and the Significant Benefit concept in the EU may on the surface look similar, but are, when taking a closer look, not comparable in how they are applied. In the EU, the significant benefit criterion may create major obstacles when developing a new drug for a rare condition where treatment options already are available. The significant benefit criterion sets a higher standard than the (for non-orphan drugs) positive benefit-risk assessment that must be demonstrated by the sponsor in the marketing approval process, which does not involve an obligation to show that such a drug is more beneficial than all other methods for treating the same condition.

Significant benefit is based on clinically relevant advantages such as improved efficacy or a better safety profile compared to existing treatments, or a major contribution to patient care (such as a new pharmaceutical form that is demonstrated to improve adherence). Significant benefit is required at the time of orphan designation, when it can be supported by preclinical studies, and at the time of marketing approval, when clinical (comparison) data are needed. Depending on the situation, either a direct or an indirect comparison between the drug and the competitive product(s) can be made. In addition, comparison must be made with other treatments in use by the patient with the orphan condition.
In the US, a clinical superiority analysis is needed for a case where the drug is otherwise the "same" as an already approved drug. This is for the same rare diseases, but there is an explanation for why the proposed variation may be clinically superior to the first drug. A drug is considered the same as an already approved drug based on properties, which vary depending on whether the drug is composed of small or large molecules. For example, small molecules with the same active moiety but different salt or ester is considered to be the same. For large molecules, "same" means a drug that contains the same, but not necessarily all, principal molecular structural features. For gene therapy products, the "same" concept is particularly challenging, and the FDA is expected to issue new guidance soon (18). In either case, if the subsequent drug was shown to be clinically superior, it would not be considered as the same drug.

The US orphan drug regulations (21 C.F.R. Part 316) define a "clinically superior" drug as "a drug...shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug (that is otherwise the same drug)" as: (1) greater effectiveness than an approved orphan drug or (2) greater safety in a substantial portion of the target population; or (3) demonstration that the drug makes a major contribution to patient care. Approvals based on clinical superiority are rare (19) and in order to successfully claim clinical superiority, comparative clinical trials would be needed.

In some therapeutic areas, like oncology, studies show that the significant benefit concept in the EU makes a significant difference in terms of drugs receiving designation or not: Among the 101 orphan-designated oncology drugs from 2008 through 2017, 40% (40/101) were approved for indications defined in part by biomarkers by the FDA, as compared with only 10% (10/101) by the EMA (20). The numbers highlight the difference in the orphan designation criteria between the regions, and that designation based on biomarkers is more difficult to obtain in the EU.

To Summarize

Having a strong understanding of the regulations that makes (and breaks) successful orphan product development, the incentives, and achievable risks, as well as knowing how to continuously enhance the product value during the drug development process, can make all the difference for successful orphan drug development. When an orphan-designated drug is eventually submitted for a marketing authorization, it must show that it continues to meet the criteria for orphan designation. It is not uncommon for products that were initially orphan-designated to lose their orphan status at this stage, despite completing lengthy research, development, and authorization processes and procedures. Measures to avoid this should be taken early. Regulatory guidance in these areas can help build a crucial framework for the overall development plan and aid in determining the fastest and/or greatest value path to market for the product.
References


18. Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2019 https://www.fda.gov/media/120341/download


Contact Information

For further information, or to discuss any aspect of PRA’s services offered please contact your PRA account director or the PRA employee below:

**Terese Johansson MSc PhD**  
Senior Regulatory Strategy Manager  
Global Regulatory Affairs

**PRA Health Sciences**  
JohanssonTerese@prahs.com

**World Headquarters**  
4130 ParkLake Avenue, Suite 400  
Raleigh, North Carolina 27612 USA

Phone: +1 (919) 786 8200  
Fax: +1 (919) 786 8201  
www.prahs.com