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Market exclusivity for orphan drugs in the US and EU

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Market exclusivity is available to developers of orphan-designated drugs to provide protection from competition after approval as a way of incentivizing development of drugs for rare diseases. In the US, developers get seven years exclusivity from the same drug being approved for the same indication. Although this was recently challenged, the US Food and Drug Administration (FDA) intends to continue restricting the scope of exclusivity to the same indication. In the EU, 10 years' protection from similar drugs being approved is available.

Keywords – market exclusivity, orphan designation, rare diseases

Introduction

There are between 5,000 and 8,000 rare diseases[1] that collectively affect 6%-7% of the population in the developed world.[2] This represents 400 million people worldwide, of which there are 30 million Europeans and 25 million Americans. Therefore, although each disease is rare, they are collectively common and finding treatments for them is a serious public health concern.[1] However, only about 130 diseases in the EU[3] and 500 in the US[4] have approved treatments. As such, there is a significant need to develop therapies for these patients. Historically, rare disease drug development was often limited by the prohibitive cost of the pharmaceutical program and the perceived low probability of successfully recouping the drug development costs. The recognition of this by regulatory authorities has led to the creation of new regulations and policies related to licensing, pricing, and reimbursement, to encourage and incentivize orphan drug research and development.

Although there are some similarities in orphan exclusivity between the US and EU, the two regions have different procedures and eligibility requirements for orphan drugs (**Table**). In the US, the Orphan Drug Act, codified in 21 CFR §316[5] provides procedures to encourage and facilitate the development of drugs for rare diseases, including the process for requesting orphan drug designation. As defined in 21 CFR 316.21(a), in the US, a drug can be considered for orphan designation if it is being developed for a disease or condition affecting fewer than 200,000 people in the US, or if the sponsor is not expected to recover development costs plus reasonable profit within seven years following FDA approval. In the EU, Regulation (EC) No 141/2000[6] (the Orphan Regulation), defines the procedure for designation of orphan medicinal products, and defines the incentives for development and marketing of orphan designated medicines. As stated in Article 3 of the Orphan Regulation, the prevalence requirement for an orphan condition is not more than 5 in 10,000 persons.

Table. Differences in orphan exclusivity between the US and EU

Main eligibility requirements for orphan designation	US	EU
Prevalence	200,000	5 in 10,000
Serious condition/unmet need	Explanation for why the drug is needed	Justification of the life-threatening or chronically debilitating nature of the condition
Significant benefit	Not applicable	Required to show significant benefit over existing treatment methods
Length of orphan exclusivity	7 years	10 years
Protection against	Same drug in the same indication	Similar drugs in the same indication
Confirmation needed of orphan designation at time of marketing application	No	Yes

Once designated, the developers of orphan drugs can benefit from pre-approval incentives. These include significant fee reductions and exemptions for various regulatory activities in the EU, and tax credits on clinical research expenses and eligibility to apply for orphan drug grants in the US. However, for many drug developers, it is the prospect of market exclusivity following approval of their orphan drug that is most attractive, protecting the drug from market competition to maximize sales. It is this incentive that is explored in more detail in this article.

United States

In the US, drug developers can get seven years of exclusive marketing rights once an orphan drug receives FDA marketing approval. There is no requirement to reapply or confirm eligibility for orphan designation at the time of licensing, so the market exclusivity is applied even if the prevalence at time of licensing exceeds the original estimate. Once the FDA grants an orphan drug designation, it can be revoked only if the application is found to contain false data or if material was omitted. This is different in the EU as described in the next section of this article.

During the seven-year market exclusivity period, other companies are prevented from marketing a product with the same active ingredient for the same use or indication as the approved orphan drug. The sameness of a drug is determined according to the definitions in 21 CFR 316.3(b)(14).[7] For small molecules, sameness involves having the same active moiety even if the ester or salt differs, and for large molecules, sameness means containing the same principal molecular structural features. The FDA has produced a draft guidance document explaining this definition in more detail for small molecules, synthetic peptides, and complex mixtures.[8] There is also FDA guidance on interpreting sameness of monoclonal antibodies[9] and gene therapy products.[10]

The FDA interprets the exclusivity provision in the Orphan Drug Act to mean that only the approved use or indication is protected, and so the same drug can be approved for a different indication during the seven-year orphan exclusivity period. However, this position was challenged in September 2021 by the US Court of Appeals for the Eleventh Circuit during a case brought by Catalyst Pharmaceuticals.[11]

Catalyst and another company, Jacobus Pharmaceutical, had both been granted orphan drug designation by the

FDA for the drug amifampridine for the treatment of Lambert-Eaton myasthenic syndrome (LEMS). Catalyst had its new drug application (NDA) approved first when they received approval in November 2018 for amifampridine for treatment of LEMS in adults.[12]

In parallel to this approval, the FDA was also reviewing an NDA from Jacobus for its amifampridine product. The agency completed its review in May 2019, but because of the orphan exclusivity granted to Catalyst, the approval of Jacobus' NDA was blocked until the exclusivity period expires.[13] However, the FDA approved Jacobus' amifampridine product for treating pediatric patients aged 6 to younger than 17 years[14] because it is a different indication to the Catalyst product and so outside the orphan exclusivity protections according to the FDA's interpretation of the Orphan Drug Act.

In the EU, approved orphan medicines are granted 10 years of market exclusivity, protecting them from competition from similar products.

Catalyst brought a lawsuit against the agency for granting the approval to Jacobus, and the court ruled against the FDA interpretation. The court's view is that the seven years of exclusivity granted to orphan drugs applies to the entire rare disease or condition, rather than being restricted to the specific indication. However, in January 2023, the agency confirmed in a Federal Register notice that, while it will abide by the court order on the Jacobus drug, it intends to continue to tie the scope of orphan drug exclusivity to the uses or indications for which an orphan drug was approved.[15]

European Union

In the EU, approved orphan medicines are granted 10 years of market exclusivity, protecting them from competition from similar products. This period can be extended to 12 years if the studies agreed in a pediatric investigation plan are completed. The Orphan Regulation also allows the market exclusivity period to be shortened if a drug becomes commercially successful, although in practice to date, this has not been done as it has been considered too difficult to provide the necessary evidence.[16]

Orphan exclusivity prevents competitors from marketing similar medicines with similar indications during the exclusivity period. Therefore, all companies should check if there are any orphan medicines authorized for the proposed indication at the time of marketing authorization application (MAA). If there are authorized orphan products, then a similarity report must be submitted with the MAA to address whether there is any similarity with the authorized product.

Commission Regulation (EC) No 847/2000[17] defines a similar medicinal product as containing a similar active substance as in a currently authorized orphan medicinal product, and which is intended for the same therapeutic indication. A similar active substance has the same principal molecular structural features (but not necessarily all of the same molecular features) and acts via the same mechanism as the approved active substance. Therefore, the similarity report included in the MAA considers the principal molecular structural features, mechanism of action, and therapeutic indication. The European Medicines Agency (EMA) offers a specific scientific advice procedure with reduced fees, known as protocol assistance,[18] to developers of designated orphan drugs. This procedure may be used to receive advice from EMA regarding similarity to approved drugs with orphan exclusivity.

The concept of having the same principal molecular structural features may not apply for advanced therapy medicinal products (ATMPs). Therefore, the European Commission has published a Q&A document to provide some information about assessing similarity between ATMPs. Certain differences in the manufacturing process which lead to a significant impact on the biological characteristics or activity of the product can result in nonsimilarity.

In contrast to the US, confirmation of orphan designation is required at time of licensing in the EU. When an MAA for an orphan medicine is submitted, a report on maintenance of the orphan designation should be included. The medicine must still meet the criteria for orphan designation at the time of marketing authorization in order to maintain the orphan designation and benefit from the 10 years of market exclusivity. An orphan designation will not be maintained if, for example, the prevalence of the condition has increased to more than 5 per 10,000 individuals of the total population, or if additional therapies have been introduced since the initial designation have improved the morbidity or mortality of a condition so it is no longer chronically debilitating and/or life-threatening. Furthermore, as the initial designation is typically based on the potential for significant benefit over existing authorized products, this should be confirmed at the time of marketing authorization.

A recent example of a medicine not maintaining orphan designation is that of the anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, Breyanzi. Breyanzi was awarded three orphan designations in 2017 and 2018 for treatment of diffuse large B-cell lymphoma, follicular lymphoma, and primary mediastinal large-B-cell lymphoma. At the time these designations were granted, the main existing treatments were chemotherapy, monoclonal antibodies, radiotherapy, and stem cell transplantations. The potential for significant benefit was based on preliminary clinical data showing efficacy in patients with refractory/released disease. However, by the time of the marketing application, several other products were approved in the relapsed and refractory populations, including other anti-CD19 CAR-T cell therapies Kymriah and Yescarta. Although the products have a similar mechanism of action involving genetic modification of patient T cells to target CD19 on tumor cells, they were not considered "similar," and so the approval of Breyanzi did not infringe upon the orphan exclusivity of the earlier approved anti-CD19 CAR-T cell therapies. However, due to lack of clinical data justifying significant benefit over these products, Breyanzi's orphan designations were withdrawn, and it does not benefit from the 10-year market exclusivity.[19]

Companies are encouraged to use protocol assistance to receive advice on the demonstration of significant benefit to increase the likelihood that the orphan designation is maintained at the time of MAA.

Conclusions and future directions

Orphan exclusivity is an important incentive for developers of drugs for rare diseases, as it provides protection from competitors and therefore gives a greater opportunity for companies to recover their investments after a drug is approved. These incentives have contributed to increased availability of treatments for patients with rare diseases.

> *Companies are encouraged to use protocol assistance to receive advice on demonstrating significant benefit to increase the likelihood the orphan designation is maintained at the time of MAA.*

In the US, seven years protection from the same drug being approved in the same indication is available, which generally provides protection from generic drug developers. In the EU, 10 years protection from similar drugs being approved is available.

Changes to the orphan legislation in both the EU and US are expected in the coming years. Although the FDA has recently confirmed that orphan exclusivity will continue to apply to the approved indication only, it is possible that more companies will use the Catalyst precedent to challenge this provision. In the EU, the European Commission published its proposed reform of EU pharmaceutical legislation in April 2023. As part of this reform, the orphan exclusivity period would be reduced to 9 years but could be increased to a maximum of 13 years for addressing a high unmet medical need, launching in all EU Member States and adding new therapeutic indications.[20]

Abbreviations

ATMPs, advanced therapy medicinal products; **CAR,** chimeric antigen receptor T-cell therapy; **EMA,** European Medicines Agency; **FDA,** [US] Food and Drug Administration; **LEMS,** Lambert-Eaton myasthenic syndrome; **MAA,** marketing authorization application; **NDA,** new drug application.

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