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Orphan drugs: Overcoming the challenges associated with developing innovative therapeutics for rare diseases.

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Recent years have witnessed significant growth in the number of sponsors developing drugs for rare or so-called 'orphan' diseases. Defined by regulatory authorities as diseases that affect fewer than 200,000 patients in the US, or no more than five in 10,000 people in the EU, orphan diseases are often genetic and therefore lifelong conditions, typically affecting patients from a very early age. While each rare disease individually impacts on a relatively small number of people, collectively, it's thought that there are more than 350 million sufferers of orphan diseases worldwide.¹

Given the need to find effective treatments for these individuals, many countries have adopted legislation to give sponsors incentives to develop drugs for orphan diseases. With increased regulatory flexibility to encourage innovation, financial incentives to offset the cost of developing drugs for small patient markets, as well as the benefits associated with significant intellectual property value of rare disease therapeutics, the industry has responded with interest and commitment. Prior to the introduction of the US Orphan Drug Act in 1983, just 38 drugs designed for rare diseases were available on the market.² Since then, more than 3,600 orphan drugs have been designated by the FDA, and over 600 have been approved.³ Global sales of orphan drugs are expected to exceed \$209 bn by the end of 2022, approximately 21 percent of the whole prescription market, excluding generics.²

While financial incentives and flexible regulatory framework present a wealth of opportunities for developers, the complexities around developing drugs for small patient populations can present significant additional challenges for sponsors. Here, we look at some of the challenges facing developers of drugs for orphan diseases, and how these can be overcome.

UNDERSTANDING REGULATORY NUANCES

Often the first consideration for developers is determining whether a disease is sufficiently rare to qualify for 'orphan' status. Orphan drug legislation varies by region, with different definitions set by each regulatory authority (Table 1). In the US, rare diseases are defined by the FDA as those that affect fewer than 200,000 people, equivalent to around six cases in every 10,000 in the population. In the EU, orphan

diseases are considered those with a prevalence of no more than five in every 10,000 people, while in Japan, the requirements are even more restrictive, equivalent to four patients in every 10,000 of the population.

In addition to different definitions for qualification, these regions also offer distinct incentives and regulatory frameworks for development. In the US for example, sponsors are granted seven years of market exclusivity following approval, whereas in the EU and Japan, this period extends for up to ten years. In the EU, two further years may be granted for those medicines with an agreed paediatric investigation plan. Various funding schemes and financial assistance are also available (Table 1).

For developers within the pharmaceutical industry it is therefore essential to understand the regulatory nuances and incentives offered by each region, in order to optimize their development strategies accordingly. By working with experts with in-depth knowledge of the global regulatory landscape and considerable experience in bringing drugs to market in each region, sponsors can maximize the opportunities available and increase the likelihood of success at the regulatory stage.

	USA	EU	JAPAN
Patient population	Fewer than 200,000 patients in US	Fewer than five cases in 10,000 in EU	Fewer than 50,000 patients in Japan
Market exclusivity	7 years from approval	10 years from approval (+2 years for drugs with an agreed paediatric investigation plan)	Up to 10 years
Financial support	<ul style="list-style-type: none"> • 50% tax credit on clinical research costs • Waiver of Prescription Drug User Fees 	Marketing application user fees waived	Tax credits and reduced fees
Funding sources	Orphan Products Grants Programme	European Commission	Government grants

ENDPOINT SELECTION AND OPTIMIZATION

One of the most common challenges experienced when developing treatments for rare diseases is the lack of information that is often known about individual conditions. With small patient populations and an even smaller number of specialist experts, limited scientific literature is typically available for researchers. As a consequence, there is often incomplete understanding around disease mechanisms, an absence of well-defined preclinical models, and a lack of knowledge around appropriate disease biomarkers. Moreover, for rare diseases without a clear path to the clinic, there is often uncertainty around regulatory-supported clinical endpoints.

To establish a firm scientific foundation on which to base clinical development efforts, sponsors often conduct natural history studies. These studies, which are typically managed in a similar way to clinical trials, can be used to provide information on how genetic and environmental variables impact on disease development and establish more accurate estimates on prevalence. They also play a vital role in developing and evaluating new clinical outcome assessments and can allow investigators to identify, assess and validate potential biomarkers with which to monitor disease progression and therapeutic efficacy.

In many cases, patients themselves are best placed to inform clinical development efforts. Today, individuals with rare conditions often share disease management strategies and knowledge of treatment options online through patient community forums and social media. To help develop a greater understanding of orphan diseases, sponsors should engage effectively with patients, their families, advocacy groups, and

clinical specialists to build a broad knowledge base. While these studies require time and resources, such investment usually results in highly valuable insight that can help to de-risk subsequent development efforts.

CLINICAL TRIAL RECRUITMENT AND RETENTION

Additional factors must be considered when designing clinical trials for rare diseases. For starters, sponsors must first identify countries with a sufficient number of study participants. Then, sponsors must find suitable study centres with the capabilities to conduct the type of trial that is required.

With both small and geographically disperse patient populations, enrolling patients in sufficient numbers to generate meaningful trial data can be challenging. Often the absence of specific patient advocacy groups can pose an additional hurdle when it comes to identifying and recruiting patients. In these cases, institutions such as the US National Organization for Rare Disorders and European Organisation for Rare Diseases, as well as patient registry programs such as the Rare Diseases Registry Program can be a vital first step in locating potential participants.

Ensuring high levels of patient retention can be a challenge for any clinical study, however this issue is even more acute for clinical trials involving patients with rare diseases. An individual patient's data can have a large impact on the outcomes of trials involving relatively small numbers of participants. To encourage retention from the outset, it is therefore important that patients, their families and carers as well as site specialists are engaged by investigators from the outset to ensure mutually acceptable study arrangements.

Participant retention can be further improved by reducing the burden on patients during the trial. Flexible and adaptable approaches should be taken to make participation in trials as easy as possible for patients and their families. Where appropriate, the use of home visits by nurses, for example, can reduce the amount of travel required, while financial and logistical support can help to minimize disruption to participants' daily lives.

FINDING THE RIGHT ORPHAN DRUG DEVELOPMENT PARTNER

The financial support and regulatory flexibility designed to encourage engagement in orphan drug research have opened up a wealth of opportunities for biotech and pharmaceutical companies. These incentives are driving the delivery of much-needed treatment options for the individuals suffering from the 7,000 or so currently known rare diseases. However, the additional considerations associated with developing medicines for conditions with small and geographically disperse patient populations can present a significant challenge, even for the most experienced drug developers.

With an often incomplete understanding of rare disease mechanisms, translational models and clinical endpoints available to developers of orphan drugs, it's often how you work, rather than what your existing specialism is, that underpins success. So when it comes to selecting the right outsourcing partner, problem solving, formulation development expertise, drug product strategy aligned with the indication, flexibility and internal framework geared toward quickly finding effective solutions are key qualities a developer should have to overcome the challenges associated with orphan drug development.

An additional challenge is represented by the small number of patients recruited in the clinical trials (sometimes in single digits for very rare disease), meaning that only few dosage units (e.g. tablets or capsules) must be manufactured. This in turn means that batch sizes of the Investigational Medical Products (IMPs) are very small and can be produced only by pharmaceutical suppliers with "miniaturised" equipment that can maintain same cGMP quality of conventional clinical trial supplies, even when working on smaller scale. Last but not least, very limited quantities or precious APIs are used to manufacture the final drug product.

REFERENCES

1. *Global Genes. RARE Diseases: Facts and Statistics. Available at: <https://globalgenes.org/rare-diseases-facts-statistics/>.*
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With a track record of success in bringing diverse range of drugs to a broad range of global markets, and with a focus on rare diseases and niche indications (orphan drugs), Evotec has the expertise and experience necessary to help achieve sponsors' goals. Our tightly integrated approach and culture of close collaboration ensures we are able to navigate development challenges and deliver innovative products to demanding timelines. By implementing the right strategies, and putting careful de-risking plans in place, it is possible to overcome the challenges associated with orphan drug development to put safe and effective medicines in the hands of the patients who need them.