WHITE PAPER PRESENTED BY PREMIER RESEARCH

Improving Regulatory and Operational Performance in Orphan Drug Development

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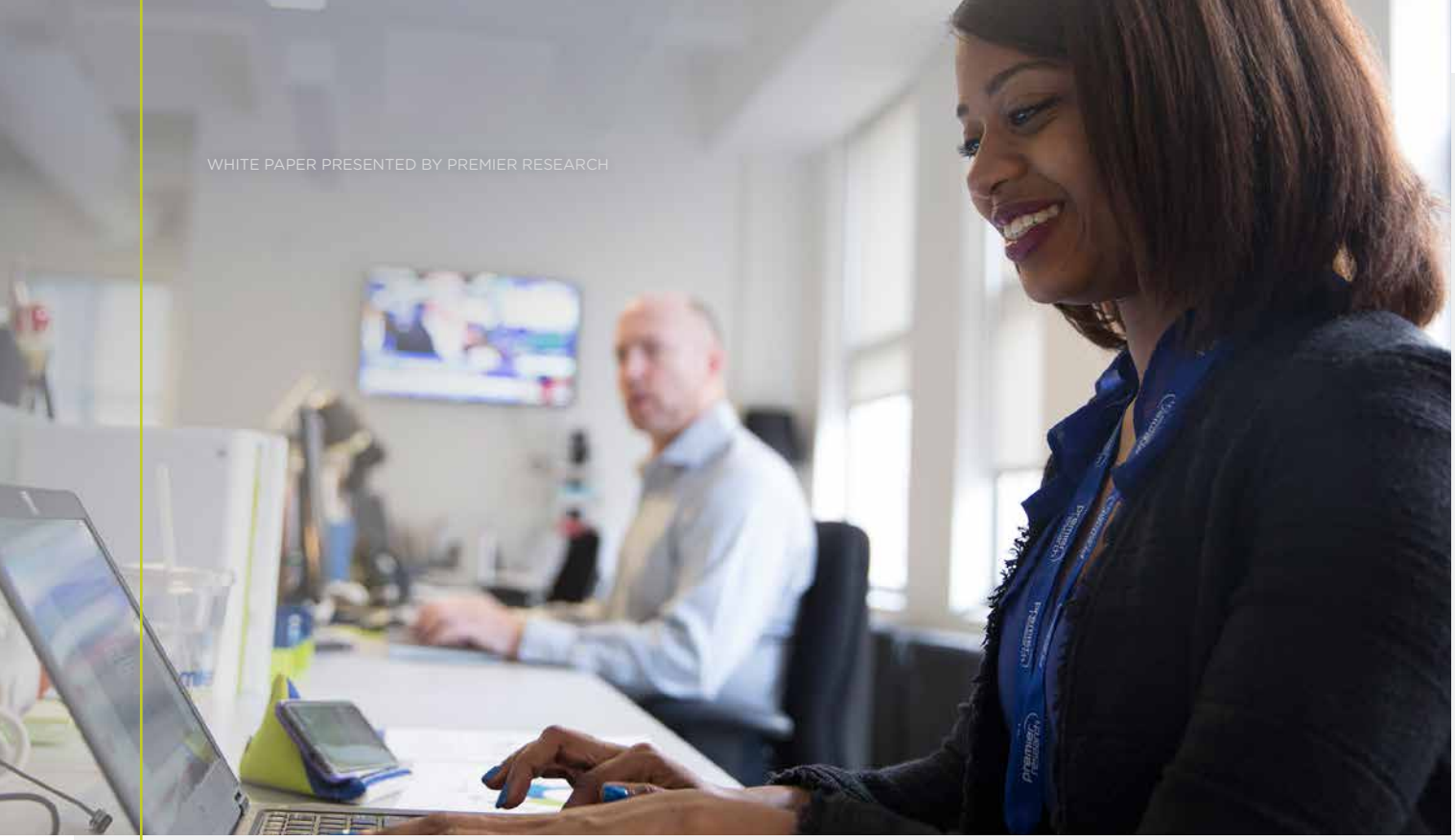
ABSTRACT

The marketplace for orphan drugs is growing, and changes in the regulatory landscape are providing favorable conditions for collaboration in the area of drug development in rare diseases. Understanding the regulatory and operational nuances of orphan drug development can help sponsors position their promising compounds for clinical and commercial success.

RARE DISEASE



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Introduction

Today, more than ever, regulatory bodies are providing a progressive platform for rare disease drug development. Extensions to existing regulations and incentives and attempts to reduce orphan drug designation applications provide an unprecedented collaborative environment for companies developing orphan drugs.

The U.S. Food and Drug Administration (FDA) is introducing new review cycles and initiatives to aid researchers, and regulators in other countries will likely follow suit with similar measures to promote orphan drug development. Understanding the regulatory landscape in orphan drug development – specifically the various pathways, incentives, and engagement opportunities with regulators – can help optimize the process and bring therapies to market faster. Sponsors stand to gain by seeking FDA engagement early and often, performing relevant studies in rare populations, and using federal grants and other available programs. All of these measures can increase the value of their companies and contribute to a growing database within the rare disease space.

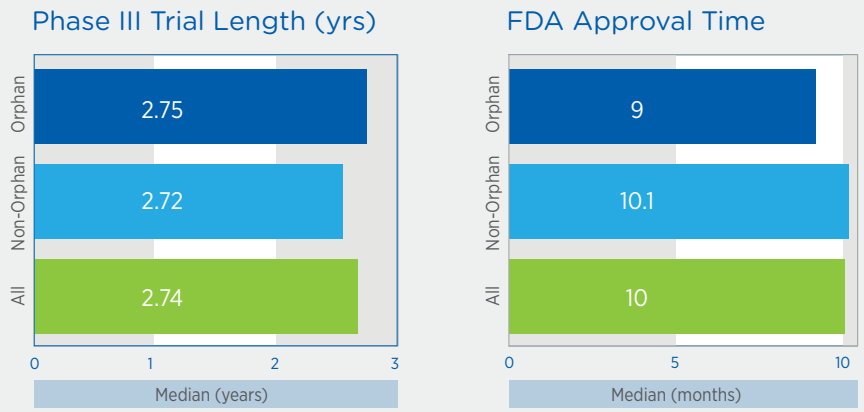
In this white paper, we explore the regulatory and operational nuances of orphan drug development, as well as the benefits of early planning and engagement and the process for operationalizing a regulatory strategy in rare diseases.

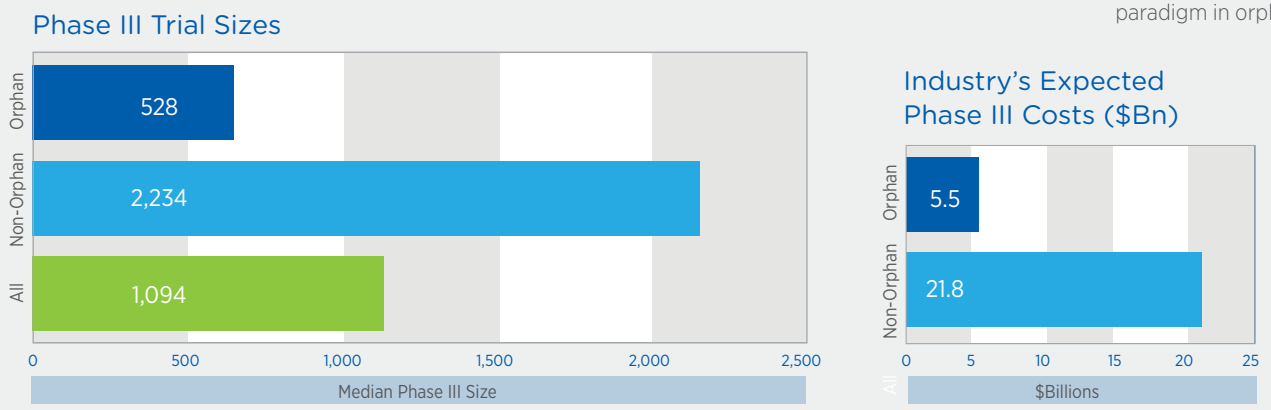
The market opportunity in rare diseases

Approximately 7,000 distinct rare diseases have been identified to date, affecting an estimated 350 million people worldwide. Since the Orphan Drug Act was passed in the U.S. in 1983, there have been nearly 2,900 orphan drug designations and more than 40 orphan drugs have exceeded $1 billion in global sales. With an estimated 250 new rare diseases identified each year, the orphan

drug market is projected to grow to $127 billion by 2018 and is expected to grow at an annual rate of nearly 12 percent per year through the end of the decade, compared with six percent for non-orphan drugs.[1]

Figure 1. Comparison of orphan and non-orphan drug Phase III trials[2]





Source(s): EvaluatePharma, 4SC/EBDC 2013 and 23 Apr 2013

In this growing marketplace for orphan drugs, there are a variety of stakeholders involved in bringing a drug to market, from sponsors, researchers, patients, and advocacy groups to investors, regulators, media, and payors. Specifically, patients and advocacy groups are playing a more prominent role than ever before, and they are taking the lead in educating sponsors and communicating with regulators about their disease experiences. The investment community has also started to take notice of the opportunity in rare disease drug development and how it can be used to augment a portfolio of development activities within a sponsor.

The smaller Phase III trial sizes required for rare diseases help lower the cost of development for orphan drugs compared with non-orphan drugs, but do not necessarily save time as there is no significant difference in the median length of a Phase III trial for an orphan or non-orphan drug. Moreover, sponsors might be surprised to learn that, despite the existence of accelerated approval pathways, the median FDA approval time for orphan drugs is not much shorter than it is for non-orphan drugs (nine months vs. 10.1 months – see Figure 1)[2]. These statistics highlight the need for improved regulatory and operational performance, creating an opportunity for rare disease sponsors to shift the paradigm in orphan drug development.

The evolving regulatory landscape

Today, changes in the regulatory landscape are providing favorable conditions for the development of orphan drugs. Fundamental knowledge of rare disease development is increasing, and the environment is ripe for collaboration, with the FDA and European Medicines Agency (EMA) mutually recognizing the need for regulatory strategies that support orphan drug development and accepting innovative approaches. This is accompanied by widespread collaboration and evidence of harmonization across other global regulatory agencies in their guidance relative to orphan drugs.

Development incentives, market exclusivity, and optimization of development pathways all contribute to paving the way for orphan drugs. Sponsors can access a number of development options for orphan drugs, which vary from region to region (see Figure 2) and should be taken into strategic consideration when developing a regulatory strategy.

Legislation such as the Food and Drug Administration Safety and Innovation Act (FDASIA) is promoting innovation to speed patient access and increasing stakeholder involvement, particularly by patients and advocacy groups. More recently, the

Figure 2. Dashboard of development options

Incentives	U.S.	EU	Japan
Product types applicable	Pharmaceuticals, Device, and Dietary products	Pharmaceuticals only	Pharmaceuticals only
Grants for research	Programs of NIH and other organizations for R&D projects	"Framework Programs" and national measures	Governmental funds
Scientific advice by regulatory authorities	Yes	Yes	Yes
Fee reductions	Yes	Yes	Yes
Regulatory tools	Fast Track, Priority Review, Accelerated Approval, Breakthrough Designation	Centralized Procedure, Conditional Approval, Exceptional Circumstances	Priority review
Financial incentives/ tax credits	50% on R&D costs, e.g., clinical studies	Managed by the member states	6% for R&D studies, limited to 10% of corporation tax
Marketing exclusivity	7 years	10 years	10 years

Sources: FDA, EMA, MHLW, 4SC/EBDC 2013

FDA put in place an Orphan Drug Modernization Plan outlining its efforts to create a more efficient, scientifically advanced, predictable, and modern approach to the approval of safe and effective treatments for rare diseases. [3]

We are also starting to see a lifecycle approach to drug development, where therapeutics developed for rare diseases are parlayed into other indications that may or may not be orphan. Orphan drug development is now being used as a platform to further research the disease and potentially expand the label. Significantly, payors are becoming more open to pricing and reimbursement discussions around orphan drugs, increasing access to these therapies.

Optimizing the regulatory pathway

After obtaining orphan drug designation for a rare disease compound, there are a variety of factors sponsors should consider for optimizing the regulatory pathway (see Figure 3). It is important to note that every stage of the development cycle is an opportunity for investor engagement.

Figure 3. Regulatory optimization pathway

Optimization of the regulatory pathways has the potential to increase revenue through sales expansion or protection, as seen in the real-life examples illustrated in Figure 4:

1. **Early access.** Starting with an orphan disease as the primary indication, followed by a subsequent non-orphan disease indication
2. **Multiple orphan drug designations.** Pursuing orphan disease designations in multiple indications
3. **Sub indications.** Starting with a non-orphan disease as the primary indication, followed by a subsequent orphan disease indication

Historically, the greatest monetary gains have come from the transition of an orphan drug into non-orphan indications.

Figure 4. Strategies for increasing revenue potential[4]

Pathways	Primary indication	Subsequent indication	Examples
1. Early access	Orphan Disease A	Non-Orphan Disease B	Avastin bevacizumab
2. Multiple OD	Orphan Disease A1	Orphan Disease A2	Glivec imatinib
3. Sub indications	Non-Orphan Disease A	Orphan Disease B	Erbitux cetuximab

Engaging with regulators

In the area of rare diseases, one size does not fit all and every development pathway is unique. Thus, it is critically important to initiate regulatory engagement early when developing and operationalizing plans for orphan drug development.

Strategies for successfully navigating the regulatory landscape include:

1. **Engaging early** and often with regulators
2. **Involving stakeholders** in the regulatory process
3. **Leading with science** to educate regulators and set new precedents
4. **Developing a global strategy**, even if budgets don't permit
5. **Developing a reimbursement strategy upfront** and demonstrating the value to regulators
6. **Creating a unique development algorithm** for each rare disease compound
7. **Innovating**, as only five percent of rare diseases currently have a treatment

Operationalizing rare disease clinical trials

There are five key areas to consider when operationalizing clinical trials within rare disease to support orphan drug designation: patient identification, patient engagement, patient retention, investigative site selection, and site team engagement.

Patient identification

Patients can be identified through:

1. **Medical informatics.** These mechanisms may include site databases, feasibility assessments, in-depth review of the disease population during the site qualification process, standard of care for the target population, and other touchpoints to raise trial awareness
2. **Key opinion leaders**
3. **Patient registries**
4. **Patient advocacy groups.** Leveraging relationships with appropriate advocacy organizations and their social media platforms can provide valuable insight into the challenges patients and their families face, which can assist with the development of operational considerations when conducting a clinical trial

Patient engagement

Patient engagement is important when developing a rare disease clinical trial. Hearing the voice of the patient allows sponsors to understand what the patient is going through, and sponsors should take advantage of the opportunity to gain that perspective. Tailoring communications so that patients and their families truly understand what it means to be involved in a clinical trial – not only the potential benefits, but also the requirements – is also essential. As many rare diseases affect children, parents are critical to the success of the recruitment process. As such, all clinical trial-related materials, including patient outreach materials, branding, and advertising, should be created with both parents and children in mind.

Patient retention

Putting patients first is the cornerstone of a successful rare disease clinical trial. One of the first steps for increasing retention is clarifying the commitment to participate. Developing participation packets or manuals can help patients and families understand the level of commitment required, and how it might impact work or school. Sponsors should also consider travel-related expenses and accommodations for patients and families when site visits are required. Providing a patient payment system is one option for addressing this issue.

Another key consideration is to acknowledge the contribution patients and families are making through periodic updates of study results or thank you notes, providing a personal touch. In some cases, it may be appropriate to solicit feedback from patients and families. When it comes to patient centricity, sponsors are encouraged to think outside the box, taking into account patients' situations and considering all the little things that could improve the clinical trial experience.

Investigative site selection

Due to the inherent complexity of rare disease trials, investigative site selection is very important. When selecting investigative sites for a rare disease trial, a good rule of thumb is to go where the patients are. This will require sponsors to identify and understand country regulatory submission requirements and Good Clinical Practice (GCP) standards for investigators and monitors in every country under consideration. Sponsors will also need to identify travel restrictions, import/export license requirements, and even the geopolitical landscape in each country. Regarding site selection, sponsors should perform due diligence on the rare disease experience and technical capabilities of prospective sites to ensure they are able to execute all study requirements.

Hearing the voice of the patient allows sponsors to understand what the patient is going through, and sponsors should take advantage of the opportunity to gain that perspective.

Site team engagement

In rare disease trials, every patient counts, so site team engagement and support are critical. In addition to regular communication and quality monitoring, thorough training should be provided at site qualification visits, site initiation visits, and monitoring visits. Where required, additional GCP training may be needed. Sponsors should also ensure that there is a succession plan for staff transitions.

Conclusion

This is an inspiring and exciting time in orphan drug development. For sponsors seeking to bring orphan drugs to market and into the hands of patients, early engagement with regulators is a critical first step. Frequent interaction with operational teams is also essential for ensuring successful study execution. Finally, involving key stakeholders throughout the entire regulatory and clinical development process, and thinking both creatively and globally around strategy, can help in optimizing the likelihood of clinical – and commercial – success.

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Nach Davé oversees Premier Research's regulatory affairs service offerings across its broad range of therapeutic focus areas, bringing to his position more than 20 years of experience in the pharmaceutical and contract research industries. He previously served the company as Director of Regulatory Affairs and rejoined Premier Research after two years as Senior Director of Regulatory Affairs at PRA Health Sciences. He also led clinical and regulatory affairs at Maxx Orthopedics, a developer of orthopedic medical devices, and has held roles in clinical operations, business development, strategic consulting, and medical affairs at companies such as Merck, Bristol-Myers Squibb, Aventis Pharmaceuticals, and Mitsubishi Pharma America. Mr. Davé holds a master's degree in drug regulatory affairs from Long Island University and a bachelor's degree in pharmacy from the Philadelphia College of Pharmacy and Sciences. He is a registered pharmacist in the state of New Jersey.

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