Customer Engagement and Information Sharing are Essential for Success in Orphan Drug Outsourcing

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Developing cost-effective manufacturing solutions for smaller volumes of highly specialized orphan drugs can be challenging, particularly for small and emerging pharmaceutical companies seeking to bring novel rare disease treatments to market. A contract service provider with experience in specialized technologies and accelerated development programs that is also committed to customer engagement, information sharing and the formation of real partnerships can be the key to achieving success.

Expanding Orphan Drug Market

In recent years, drug makers have shifted their focus from the development of blockbuster drugs to the development of therapies to treat rare diseases, also known as "orphan drugs." There have been 7000–8000 rare diseases identified to date; effective medicines have been developed for only a few hundred of these diseases.

A number of unique clinical, regulatory and commercial challenges are associated with the development of therapies for the treatment of rare diseases. In recognition of these challenges, legislation has been implemented in the United States, the European Union and elsewhere to provide regulatory and financial incentives aimed at stimulating investment in orphan drugs.

Since the implementation of the U.S. Food and Drug Administration's (FDA) orphan drug modernization plan in 2017, the approval rate for orphan drugs in the United States has accelerated significantly.[1] Despite the reduction of the Orphan Drug Tax Credit in 2017, the number of new orphan drug approvals continues to hit new records.[2] In Europe, orphan drug approvals by the European Medicine Agency (EMA) more than doubled in 2017 to 17 in 2018.[3] Notably, 40% of the innovative drugs undergoing clinical trials for potentially new targets in mid-2018 were developed to treat rare diseases.[4]

Not surprisingly, the growth rate for the global orphan drug market is quite healthy. Pharmaceutical intelligence firm EvaluatePharma estimates that it is expanding at a compound annual growth rate of 12.3%, which is nearly twice the growth rate for the overall pharmaceutical market.[5] By 2024, the orphan drug market will be valued at $262 billion, and sales of orphan drugs will account for one-fifth of worldwide drug sales and approximately 30% of total R&D pipeline sales through that year.

Growing Use of CDMOs

With knowledge of disease mechanisms continuing to expand, novel drug targets are being discovered regularly. Lower development costs for rare disease therapies combined with limited or no generic competition create incentives for drug manufacturers positioned to manage the complexities of the development and commercialization process.

Recent successes in the development of orphan drugs coupled with productivity challenges in the classic pharma R&D model for indications with a higher prevalence have resulted in a number of major pharmaceutical companies establishing business units focused on rare diseases. Investment by venture capital companies in early-stage biotechs with rare disease programs has also increased.

In many cases, the firms developing orphan drugs are small and emerging pharma and biotech companies with missions aimed at developing targeted therapies for specific disorders. The Tufts Center for the Study of Drug Development reported that smaller pharma and biotech firms developing small molecule drugs have higher clinical approval success rates than large companies.[6]

These smaller firms are achieving those successes by leveraging partnerships with effective contract development and manufacturing organizations (CDMOs) that support the unique set of needs that arise during development and commercialization of orphan drugs. These companies rely on CDMOs for expertise in manufacturing, process and formulation development, validation and regulatory compliance.

Orphan Drug Development Challenges

A fundamental challenge in drug development for the majority of rare diseases is that there is often relatively little known about the pathophysiology or the natural history of these diseases. Typically, there are only a small number of experienced clinical investigators worldwide and in contrast to more prevalent diseases, there is relatively little published scientific literature.

The most obvious challenge in conducting clinical trials in rare diseases is the small numbers of patients available for clinical studies. Enrollment of patients into clinical studies in sufficient numbers to generate meaningful comparative data is difficult and usually requires the participation of many sites across diverse geographies, frequently with only very few patients enrolled at each site. Delays in the recruitment process often occur, adding cost and uncertainty to these programs.

CDMO Concerns

It is difficult, in some cases, for CDMOs to commit to projects involving orphan drugs, not only due to the small volumes of product units that are often needed, but also the uncertainty deriving from the lack of deep knowledge about the targeted diseases.

Understanding and Aligning Commercial Strategies

While many CDMOs are disinclined to pursue small-volume projects focused on developing and manufacturing orphan drugs for unmet needs, others, such as Grifols, actively seek out such projects with small and emerging pharma companies. The key to successful project completion is to develop an understanding and alignment of the commercial strategies of both organizations.

CDMOs must understand the commercial strategy of the sponsor to be able to accurately structure the timeline and to guarantee production of the product on time. Many orphan drugs are awarded accelerated approval designations, leading to the need to implement projects in dramatically shortened timelines. In addition, knowledge of the sponsor's commercial strategy allows the CDMO to better support management of its life cycle and prepare for new market demands.

Sponsor companies developing orphan drugs must, in turn, understand the requirements of their CDMO partners. Most importantly, it is essential to agree on a minimum quantity of product for scale-up as the orphan drug advances through each development stage. This type of agreement is particularly crucial when the CDMO must invest in new equipment and technologies specifically for the project, which impacts production costs. The CDMO must also have the capability and flexibility to produce both very small volumes and larger volumes when demand increases.

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Open Communication is Essential

Guaranteeing that timelines are met also requires honest, two-way communication between the CDMO and the sponsor firm from the beginning of a project. A basis of mutual trust must underlie this communication, resulting in the generation of a true partnership rather than a mere customer-supplier transaction.

Such a partnership can only develop when the individuals that make up the different teams at the CDMO and the sponsor company — including representatives from R&D, Quality, Regulatory Affairs, Manufacturing, Business Development and Business Intelligence — are perfectly aligned and committed to working together. Only under these conditions is it possible to effectively manage the complexities of orphan drug

development programs and move them forward meeting all expectations, particularly if unexpected difficulties and complications arise.

Before initiating a project, the CDMO should be provided with information about potential competitors, evolution of the market, regulatory aspects and patient needs to confirm the viability of the program. The sponsor company must also be willing to share all of the relevant technical process information for each phase of the project, whether the program begins at the development stage or with technology transfer of an established process and product.

During the technical transfer process, the CDMO should welcome the presence of representatives from the sponsor company with expertise in the specific product involved. The efficiency of tech transfer can be greatly increased when technical experts can directly advise CDMO operators and engineers about the details of the process. Grifols welcomes training of plant personnel by sponsor company experts and has found that doing so often leads to reduced project timelines.

Once a project is initiated, regular, frequent communication between multidisciplinary team members from all areas must take place to ensure constant sharing of information and to enable the generation of new ideas and anticipation of possible scenarios that may hinder the progress of the project.

An effective CDMO also recognizes the importance of quickly sharing information with their partners when unexpected difficulties like equipment problems or test lab issues arise. Only with direct and immediate communication can optimal solutions be developed and implemented. Ongoing communication is needed to keep the customer updated on the implementation of the solution and resolution of the issue. Finally, maintaining honest and real communication with the client is crucial for CDMOs in the effort to reduce potential risks in both the development and technology transfer stages.

Risk Assessments are Foundational

Sponsor firms developing orphan drugs as parenteral products should only work with CDMOs that have the necessary expertise to produce these complex products and those that are committed to conducting extensive risk assessments before beginning any new project.

The performance of a comprehensive risk analysis is crucial to the development of effective processes for sterile injectables. These risk analyses allow for identification of sources of potential problems along with implementation of measures that may prevent those issues from arising. The goal of risk management is not to eliminate downside risks, but to control them within an acceptable range. Once the limits and potential areas of concern have been identified, the next step is to determine the process conditions and controls needed to ensure that the process will be robust and scalable. Orphan drugs are typically very high-value products. Risk assessments can also help identify optimal solutions for minimizing any loss of the expensive API.

Collaborating with Grifols

Grifols specializes in the terminal sterilization manufacturing of parenteral products. We are also a CDMO business unit positioned within a large, international pharmaceutical company with extensive experience in the development and commercialization of many types of sterile drug products. As such, Grifols has access to financial, technical, regulatory and other resources not readily available to standalone CDMOs, and we remain sufficiently flexible as an ideal partner for small and emerging pharma companies.

While the CDMO business at Grifols is focused on meeting the needs of smaller customers, we maintain access to the resources of our parent company. As a result, we are often able to make investments in equipment and technology for specific projects and are willing to establish a range of commercial arrangements customized for each project and client.

In addition, the equipment used for our CDMO partners is the same equipment used for internal projects, designed specifically for Grifols by Grifols Engineering. This vertical integration fits with Grifols' quality culture and enables us to control the entire process, ensuring achievement of the highest quality.

We are able to leverage the resources and experiences of the larger Grifols organization to provide significant value to our partners, from guiding new drug applications through regulatory approval to determination of patient and caregiver reactions to product delivery systems.

We can also advise our partners on the best container choices based on the intended patient population. We have been working directly with nurses and doctors for decades and understand their preferences regarding parenteral product design. As a result, Grifols can assist clients in selecting the most appropriate containers and delivery systems that will provide the greatest ease of use and ultimately the highest level of patient adherence.

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