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CMC Best Practices: Expediting Orphan Drug Development to Combat Rare Disease

More than 25 million Americans are affected by one of 7,000 rare diseases (a disease affecting fewer than 200,000 Americans) – of which 90 percent have no FDA-approved treatment, certainly a sobering finding from the National Organization for Rare Disorders (NORD). This February 28 marks the global observance of Rare Disease Day, a day when we participate in raising awareness and generating change for the global population and their families living with rare diseases.

Orphan Drug Development: Key to Treatments for Rare Diseases

Historically, pharmaceutical companies have been reluctant to pursue therapeutics for rare diseases given the high costs and very small patient populations. However, changes to laws and regulations encouraging development of therapies for rare diseases over the last few decades have had a positive impact, and orphan designation now confers sizable incentives. These include:

- shortened clinical programs
- fee waivers
- expedited approval pathways (e.g., Fast Track, Accelerated Approval, Breakthrough Therapy) tax credits
- longer market exclusivities

While these incentives and the work of advocacy groups have led to a significant increase in orphan drug applications, rare disease drug development programs continue to face obstacles – from clinical trial recruitment and design to drug pricing and a lack of reimbursement pathways.

In spite of these obstacles, however, drugmakers have clearly embraced orphan drug development. Worldwide, nearly a third of drug pipelines target rare diseases, and share of new drug approvals for rare diseases doubled from 29% of all approvals in 2010 to 58% in 2018, according to the Tufts Center for the Study of Drug Development.

Challenges for Expedited Drug Development Programs

Speeding up development, approval and time-to-market are compelling incentives but expedited development programs also carry some risk. In our white paper, Orphan drug development a pragmatic approach to developing a rare disease drug, we explored some of the issues which are unique to development programs operating on expedited timelines.

Condensed Timelines
Compared with traditional drug development paths, orphan drug programs typically shorten time-to-market by 3-8 years. This means balancing the risk of executing less process development and optimization to gain earlier access to the drug. However, some elements of chemistry, manufacturing, and controls (CMC) simply cannot be compressed, such as stability programs or validation work – further heightening the strain on timelines.

Limited Funding
Many small biotech companies have limited funding, and expedited programs typically require significant CMC investment. In some ways, orphan drug development works inverse of traditional drug development. Typically, more money is allocated to CMC as clinical milestones are achieved and program risk declines. With orphan drugs, the runway is much shorter. This requires more investment in CMC earlier, before successful clinical data has lowered the risk.

Since timelines are so compressed, once positive clinical results free up more funding, the next challenge fast becomes the speed needed to address necessary CMC requirements in time to meet filing and launch deadlines.

Rapid timelines for the expedited programs also place tremendous pressure on CDMOs collaborating with a drug sponsor. It is often the expectation for the CDMO to solve complex chemistry problems under aggressive timelines, but with limited funding from the drug sponsor.

Supply Chain Stressors
Situations such as the COVID-19 pandemic have caused extreme stress on supply chains across the globe, and not just in the pharmaceutical industry, as discussed in our white paper, The shift toward US pharmaceutical manufacturing: considerations in attaining the right global mix .

The lessons learned during the pandemic are apt, as orphan drug development programs require rigorous attention to both forecasting and supply chain risk minimization strategies to ensure you meet finished dosage supply requirements at launch.

Orphan drug sponsors and their CDMOs must have contingency planning for raw material shortages, facility changes, equipment downtime, and surges in product demand. Planning should incorporate elements such as dual sourcing (preferably in different geographies with distinct supply chains) and raw material stockpiling to assure uninterrupted supply. Plans should also include optional backup manufacturing sites capable of supporting production.

Early Interaction with Regulators
Successful compression of a development timeline for an orphan drug candidate demands early contact with regulators. In fact, highly effective CMC teams initiate interactions with the FDA or other relevant regulatory agencies as soon as possible. Early insight can prove invaluable for both sponsors and their CDMO partners, who can then rapidly and proactively plan a campaign to develop an efficient and cost-effective manufacturing process and supply chain strategy for commercialization.

It is important for drug sponsors to understand the unique challenges that can arise when developing orphan drugs on an expedited timeline. Sponsors and CDMOs, in collaboration together, must balance the risk of less process development vs. earlier access to the drug – and robust planning and preparation are essential if you are to succeed in CMC development.

ABOUT CURIA

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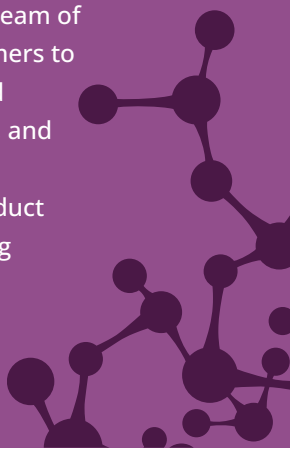

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