Article

Exceling at Accelerating in Rare Disease Drug Development

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According to the National Institutes of Health, more than 30 million people in the United States are affected by a rare disease. Defined in the Orphan Drug Act as any disease that affects less than 200,000 people in the United States, rare diseases total more than 7,000 conditions. This means that based on 2020 census records, nearly one in 10 Americans is living with a rare condition, making seemingly "rare" diseases more common than ever before.

Due to the genetic nature of most rare diseases, 75% of them affect children and can be life-threatening. About a third of affected children will not live to their fifth birthday. In fact, rare diseases cause 35% of deaths in the first year of life. Small patient populations can mean there are limited resources, support and information available to detect a meaningful signal in a rare disease. Also, people living with rare diseases often struggle to receive the appropriate diagnosis due to low awareness and understanding. Typically, people with rare diseases are misdiagnosed two to three times before being diagnosed correctly. On average, proper diagnosis from the time of first symptoms takes about five years.

Compounding these issues, only about a tenth of rare diseases currently have a US Food and Drug Administration (FDA)-approved treatment available. While there has been an upward trajectory in the percentage of drugs approved to treat rare or "orphan" diseases over the past decade or so, there remains a significant unmet need for FDA-approved therapies for these conditions.

Running up that hill

Rare disease drug development can be complex for many reasons and poses a range of clinical, regulatory and commercial challenges. Of course, innovative approaches, collaboration and engagement are necessary for any drug's development. However, in the case of developing rare disease treatments, the need for innovation is critical due to the limited information available. For example, if there are only a handful of patients in the entire country or the entire world with a condition, the information related to statistics, data sets, number of patients exposed and treatment experience is unfortunately not at the same scale as information that is available for other, common conditions. With orphan diseases, it is also often difficult to set clinical endpoints, biomarkers and outcomes measures. Similarly, sensitive patient subpopulations ranging from neonates and children to adults with co-morbidities make conducting clinical trials ethically problematic. There is also investor hubris in that there is an overuse of the FDA's accelerated approval pathway and the choice of biomarkers may limit a full approval.

Pushing fast forward on drug development for rare disease

Thankfully, there are important new initiatives underway to address these obstacles and opportunities. The FDA's Center for Drug Evaluation and Research (CDER) recently launched its Accelerating Rare disease Cures (ARC) Program to support rare disease drug development. Looking to harness CDER's collective expertise and activities, this program is meant to speed up and increase the development of effective and safe treatment options addressing the unmet needs of patients with rare diseases.

One of the greatest challenges in rare disease drug development is being able to gather enough data to have a solid endpoint and an agreement with regulators to move forward with a program. To overcome this challenge, the FDA has funded the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP®), a separate initiative to provide a centralized and standardized data hub from a variety of sources that can inform rare disease characterization and clinical trial design and answer critical questions in rare disease drug development.

The RDCA-DAP initiative is an important step forward, as the platform provides an integrated database and analytics hub designed to promote the secure sharing of existing patient-level data and encourage the standardization of new data collection. By integrating such data in a regulatory-grade format suitable for analytics, RDCA-DAP accelerates the understanding of disease progression, clinical outcome measures and biomarkers, and facilitates the development of mathematical models of disease and innovative clinical trial designs.

FDA recently announced collaborations for lysosomal storage disorders, marking the first step within the ARC initiative that is disease centric.

Supplementing with virtual patients

When developing treatments for rare diseases, there are several things manufacturers must consider. For example, given the limited knowledge in rare diseases, the use of modeling and simulation can reduce uncertainty in both technical and regulatory success and potentially accelerate rare disease drug development. Model-informed drug development (MIDD) approaches can help model human systems, pharmacokinetics, pharmacodynamics and health economics derived from preclinical and clinical data sources. Because MIDD can also incorporate real-world evidence (RWE) along with data from trials, researchers can use it to support clinical trial design and observational studies to generate better treatment approaches in rare disease. Similarly, healthcare systems may use RWE in MIDD to substantiate coverage decisions.

For rare diseases in particular, quantitative systems pharmacology can be applied to aid mechanistic understanding and offer hypothesis-generating opportunities in cases in which information gaps may limit using more empiric approaches. Similarly, these quantitative methods can be used to interpolate or extrapolate dose and response where there are challenges in exploring dynamic dose ranges in clinical trials, as is often the case in pediatric and rare diseases.

Physiologically based pharmacokinetic (PBPK) modeling may also be used to determine what effects a drug may have on the body with minimal data. This includes drug-drug interaction screening and first-in-human dose prediction, which can reduce the number of clinical studies performed or patients enrolled in trials in a rare disease program.

For example, Alagille syndrome is an inherited condition in which bile builds up in the liver because there are too few bile ducts to drain the bile. Alagille syndrome has been estimated to occur in approximately 1 in 30,000–45,000 individuals in the general population. Pruritus, or chronic itchy skin, is a symptom of cholestasis in Alagille syndrome, which can lead to self-mutilation, scarring and sleep deprivation in children affected by this rare disease. For some families, the severe debilitating itch associated with Alagille syndrome can cause significant suffering and may affect their quality of life or lead to depression or family disruption. Many children may require major surgical interventions such as liver transplantation for refractory pruritus.

Due to the small number of patients in the United States, quantitative approaches including non-compartmental analysis, dose-response modeling and PBPK modeling were instrumental in predicting drug exposure and dosing, and for designing the clinical trial for pruritus in Alagille syndrome. These methods ultimately helped to advance a successful rare disease therapy for pruritus that was approved by the FDA in 2021, providing some relief and hope to families living with Alagille syndrome.

By leveraging clinical pharmacology, MIDD and regulatory expertise, rare disease drug developers can help de-risk their programs and accelerate bringing safe, effective, new treatments to patients and families in need.

Effective drug development for rare diseases can happen only through innovation, collaboration and education. The FDA's ARC program and RDCA-DAP are a step in the right direction and will help to accelerate rare disease drug development, but more work needs to be done to address the needs of patients with rare diseases and their families.

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