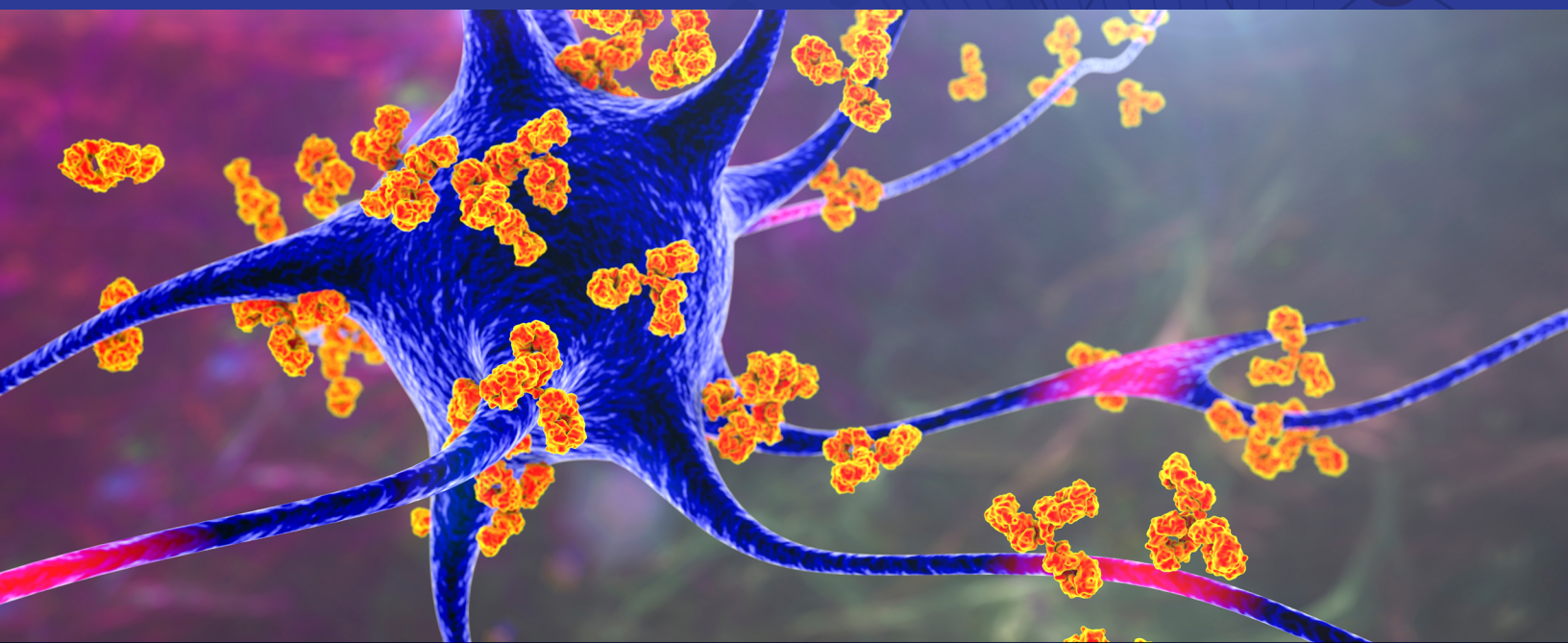


The Challenges and Opportunities of Rare Disease Drug Development



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INTRODUCTION

New therapeutics development in rare diseases presents both opportunities and complexities. Because of the small patient pool available in these indications, there are challenges in designing and conducting clinical trials and the data interpretation that follows, and the ultimate path to registration. The top 3 critical downfalls in rare diseases development include 1) poor understanding of the disease process and natural history, 2) incomplete understanding of clinically meaningful endpoints, and 3) inability to assess clinical benefit and achieve full approval. This whitepaper reflects on some of these challenges and opportunities in rare diseases drug development.

A central feature in rare diseases development is that the clinical studies are conducted in small patient populations. The US FDA does not preferentially treat rare diseases in comparison with common diseases. Thus, regulators expect the same criteria for assessing safety and effectiveness. For example, the FDA requires that adequate and well-controlled investigations dictate the basis for effectiveness of new drugs.

Moreover, no two rare diseases are created equally, especially across the therapeutic areas. Therefore, the regulatory frameworks of approval might vary across oncology and non-oncology areas. Given the complexity of performing clinical trials with small patient populations, trial enrichment considerations should include the type/subset of disease identification to enroll, the stage of disease progression of interest, and whether there are clinically meaningful end points to discern treatment effect. In the latter instance, understanding the biomarkers and surrogate endpoints early in development is prudent.

DEFINITIONS

There is no universally accepted definition for rare diseases (Figure 1). Each region/country has its own legislative framework to define prevalence rates for rare diseases. For example, the US FDA, EMA, and other regulators have operational threshold criteria for rare diseases (see Table 1).

Table 1.

Prevalence criteria used by regulatory agencies to define rare diseases

Regulatory agency	Prevalence criteria	Reference
US FDA	200,000	Orphan drug act, 1983
EMA	5/10,000	EC 141/2000
Japan PMDA	50,000	JPMA, 2008
Australia	2000	Therapeutic goods act, 1989

Recognizing even rarer diseases than the prevalence regulators recognize, the National Institute for Health and Care Excellence introduced an “ultra-rare” disease subcategory, where the prevalence rates are <1 per 50,000 individuals. Another common definition that often is synonymous with rare diseases from a policy perspective is “neglected diseases,” for which there is no universally accepted definition. In principle, neglected diseases are regional tropical diseases in low- and middle-income group countries and regions lacking scalable interest and incentives for drug development or access. This whitepaper will focus on the US regulatory framework.

BIOLOGY AND GENETICS OF RARE DISEASES

Nearly 80% of rare diseases have a genetic etiology (IOM, 2010; NORD, 2007; NIH, 2008). This shouldn’t be interpreted as an identifiable or easily tractable mechanism because most such diseases lack understanding of molecular pathogenesis. However, for the small incidence where molecular pathogenic pathways are well understood, a single gene defect causes the disorder. In that case, that genetic defect remains a good candidate for therapeutic modification, regardless of modality. Examples include alpha1- antitrypsin deficiency (causing serious inflammatory disease), Friedreich’s ataxia (causing neurological disorders), hexosaminidase A (15q23) [causing Tay-Sachs], and Huntington (4p16) [causing Huntington disease]. Contrast these with Fanconi anemia, which have several underlying named variants, each caused by a defect in a different gene (D’Andrea, 2010) and muscular dystrophy, which has several major forms, one of which includes Duchenne muscular dystrophy for which many companies have active drug development interest.

Figure 1.

Rare diseases represent significant unmet medical need

**OVER 7,000
RARE DISEASES IDENTIFIED**

**RARE DISEASES AFFECTS MORE THAN
350 MILLION PEOPLE
WORLDWIDE**

**APPROXIMATELY
OF CHILDREN
WITH THESE
DEBILITATING DISEASES WILL NOT
LIVE TO SEE THEIR 5TH BIRTHDAY 30%**

**APPROXIMATELY
80% OF RARE
DISEASES
ARE GENETIC 80%**

ONLY 5% OF RARE DISEASES HAVE AN FDA APPROVED DRUG
50% OF PEOPLE AFFECTED BY RARE DISEASES ARE CHILDREN

Whereas single gene defects appear more plausible, for many other rare diseases, multiple genes are hypothesized to be collectively responsible for the disease manifestations (Dale and Link, 2009; IOM, 2010). This includes the Williams-Beuren syndrome wherein one gene was identified as causing cardiovascular issues, and multiple other genes had overlapping features of the disease (Pober, 2010). For non-genetic, heritable diseases, sarcoidosis is a good example. However, to date no specific underlying genetic mutation has been identified. Because of lack of research incentives, the genetics of many rare diseases remains poorly understood.

Despite a vast prevalence of genetic defects within rare diseases, not all genetic targets are druggable (Finan et al 2017). There are several emerging methodologies such as artificial intelligence and machine learning (Brasil et al., 2019), genomic analysis and next generation sequencing (Brasil et al., 2019), and translational bioinformatics (Schadt et al., 2005; Vodovotz et al., 2008), which could be all used to elucidate the molecular networks and pathways underpinning rare diseases. Indeed, some drug discovery technology companies have invested in such biomarker-based drug discovery platforms. Such platforms can help deconstruct complex biological themes, using data from gene expression arrays, proteomics studies, and importantly clinical observations from patients with rare diseases to identify molecular signatures of disease mechanisms (Dudley et al., 2009; Patel et al., 2010; Suthram et al., 2010). Such information coupled with heat signatures of drug responses could assist in rational drug discovery and development programs for rare diseases (Schadt et al., 2005b). Basic drug discovery research is the first step to identifying a causative hypothesis – which could be a gene alteration/defect, biochemical enzyme pathway, epigenetic mechanism, etc. – following which drug traction can occur in identifying treatments for rare diseases.

These uncertainties in biology and genetics complicate selecting and choosing biomarkers and surrogate endpoints, as not all biomarkers are in sequence to the disease progression and may not predict clinical benefit. Sponsors should select their biomarkers carefully as it may affect the ultimate probability of successful registration.

LEVERAGING REGULATORY FRAMEWORKS AND REDUCING REGULATORY UNCERTAINTY

The mid 1980s saw the evolution of parallel regulatory initiatives around the world that recognized rare diseases but also provided guidance for sponsors interested in developing products for such diseases. For example, the US Orphan Drug Act defined rare diseases but also conferred seven years of market exclusivity from date of approval, together with tax incentives, fee exemptions, and priority review vouchers for sponsors.

The US FDA has a page devoted to rare diseases development (<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/rare-diseases-program>) where sponsors can find a 1-stop resource. The FDA pre-IND meetings can be used to leverage agency inputs on the rare disease development strategy. Such pathways are still widely underutilized. Use them to reduce the uncertainty in drug development while getting agency experts' input on your development strategy. This is the first opportunity to negotiate and discuss clinically meaningful endpoints.

The FDA has many options to expedite drug development for medically unmet serious and life-threatening conditions, and these include—fast track status, accelerated approval, and priority review. These frameworks expedite reviews and guidance to sponsors on the nature of the evidence necessary to achieve approval (FDA, 2009a; Schadt and Thomas, 2009).

- For fast-track applications, sponsors submit electronic common technical document (eCTD) modules of an NDA on an ongoing basis for a “rolling review” by the FDA. This pathway allows more iterative consultations with FDA on various drug development considerations related to the entire application for approval. In this staggered submission approach, all other submitted modules are completed as the final clinical trials are concluded, reported, and reviewed.
- Another option is accelerated approval, which allows sponsors to use surrogate endpoints if they meet the criteria of “reasonably likely to predict clinical benefit.” The FDA defines surrogate endpoint as “a laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy” (57 Fed. Reg. 13234 at 13235; Fleming, 2005; IOM, 2010). However, the FDA then requires post-approval studies to confirm risk/benefit based on clinical outcomes.

While rare disease developers have actively pursued accelerated approvals, this approach is fraught with challenges. Full conversion is expected. If the biomarker/surrogate endpoint doesn’t translate into clinical efficacy, the approval will be withdrawn. Drugs approved under this mechanism have inconclusive evidence of safety and benefit until post-approval requirements are lifted (Fleming, 2005). When Pfizer withdrew gemtuzumab ozogamicin (Mylotarg) in 2010 after a post-approval study failed to demonstrate benefit, it highlighted the issue of lack of conversion. At least four oncology drugs have lost indications in 2021 due to lack of conversion.

- Another mechanism is priority reviews, wherein the FDA completes reviews within six months compared to a standard ten-month review. Orphan drug applications leveraging this pathway have significantly increased (Tufts Center, 2010). The FDA may also award priority review vouchers when approving a drug for a neglected tropical disease.

CHALLENGES IN THE ACCELERATED APPROVAL MECHANISM

Duchenne muscular dystrophy (DMD) is a rare genetic disorder that causes progressive muscular degeneration. While many mechanisms have been postulated for DMD, the majority pathways suggest that the weakness arises due to alterations of the dystrophin protein which is essential for muscle integrity. Loss of dystrophin causes an imbalance of the dystrophin-associated complex leading to muscle fiber deterioration with associated inflammation. The progressive muscle wasting leads to loss of ambulation by around 12 years of age and death by early adulthood. There are currently at least four approved drugs using the accelerated approval pathway that have yet to be fully converted. Table 2 lists the salient features of these “dystrophin based” approvals.

Table 2

Accelerated approvals for DMD

Drug	Modality	Surrogate Endpoint	Clinical data
Eteplirsen (EXONDYS)	Antisense oligonucleotide; exon 51 skipping	Increase in dystrophin	Primary endpoint was dystrophin production No change in 6-minute walk test (6MWT) Median increase in dystrophin after 48 weeks was 0.1%.
Golodirsen (VYONDYS53)	Antisense oligonucleotide; exon 53 skipping	Increase in dystrophin	Median change in dystrophin from baseline was 0.88%
Viltolarsen (VILTEPSO)	Antisense oligonucleotide; exon 51 skipping	Increase in dystrophin	Median change in dystrophin from baseline was 1.9%
Casimersen (AMONDYS45)	Antisense oligonucleotide; exon 45 skipping	Increase in dystrophin	0.59% increase in dystrophin

Source: FDA summary basis of approvals

Notably, eteplirsen's clinical study was powered for an effect on the 6MWT, and it found no significant difference from placebo in an open label extension for four years. This drug highlights some of the inherent challenges in the accelerated approval mechanism whereby full conversion is essential for approval.

The choice of biomarkers and qualifying them depends on several factors. They include relationship to the pathophysiology of disease, understanding whether changes in those biomarkers yield clinically meaningful benefits, predictivity of those biomarkers, as well as the necessity of ensuring validation/qualification of biomarker assays so that there is biological stability.

CERTARA'S APPROACH TO RARE DISEASE DRUG DEVELOPMENT

We offer three key segments of rare diseases drug development expertise: (1) clinical study design, clinical pharmacology and science, and choice of endpoints, (2) quantitative methods, and (3) regulatory strategy and payer frameworks. The common denominator for these segments is technology-enabled model-informed drug development (MIDD). In short, MIDD uses models of human systems, pharmacokinetics, pharmacodynamics, and health economics as well as the interconnectedness of such models to advance drug development. Our experts collaborate with clients to offer end-to-end tangible solutions for rare diseases (Figure 2).

Figure 2.

Certara rare disease therapeutic expertise.

Genetic & Hereditary	Gastrointestinal	CNS	Bone & Muscle Disease
<ul style="list-style-type: none"> Fabry Disease Pompe Disease Hunter's Disease Metachromatic Leukodystrophy Disease Transthyretin-mediated Amyloidosis Urea Cycle Disorder Hereditary Angiodema ACE-induced HAE Lennox-Gastaut Syndrome 	<ul style="list-style-type: none"> Familial Mediterranean Fever Gaucher Disease Cystic Fibrosis Hypophosphatasia Chronic Liver Disease Huntington's Disease Dravet Syndrome Thrombocytopenia Hereditary Transthyretin-mediated Amyloidosis 	<ul style="list-style-type: none"> Short Bowel Syndrome Pediatric Crohn's Disease Carcinoid Syndrome 	<ul style="list-style-type: none"> X-linked Hypophosphatemia Duchenne Muscular Dystrophy Hypophosphatasia
Antinfectives/Antivirals	Oncology	Blood Disorders	Other
<ul style="list-style-type: none"> Anthrax Orthopoxvirus/Smallpox 	<ul style="list-style-type: none"> Acute Lymphoblastic Leukemia Metastatic Myeloma Multiple Myeloma Acute Myeloid Leukemia Urinary Bladder Cancer (Photodynamic Therapy) BRAF Mutation Blood Cancer Ovarian Cancer 	<ul style="list-style-type: none"> Myasthenia Gravis Restless Leg Syndrome Spasticity due to Multiple Sclerosis PKAN (Pantothenate Kinase-associated Neurodegeneration) Friedreich's Ataxia 	<ul style="list-style-type: none"> Radiation Poisoning Hypoparathyroidism Molybdenum Deficiency Peyronie's Disease Hyperuricemia in Patients with Gout Refractory Hepatic Veno-occlusive Disease Onchocerciasis Neglected Tropical Diseases

CASE STUDY #1: DISEASE PROGRESSION MODELING

Given large phenotypic variability in rare diseases and the general challenges with choice of biomarkers of disease pathophysiology, it's important to model the course of disease progression. For example, Perrone and coworkers (2017) developed a drug development tool based on observational data collected over multiple decades to understand estimated glomerular filtration rate (eGFR) decline and end-stage renal disease (ESRD) in patients with autosomal dominant polycystic kidney disease. The study augments data from animal and human studies that supported the use of total kidney volume as a prognostic endpoint of choice in clinical trials for this disease. Their findings suggested that patients with larger total kidney volume are more likely to progress to a 30% decline of eGFR within the course of a clinical trial, leveraging the model as a tool to aid trial enrichment and maximizing information (Figure 3).

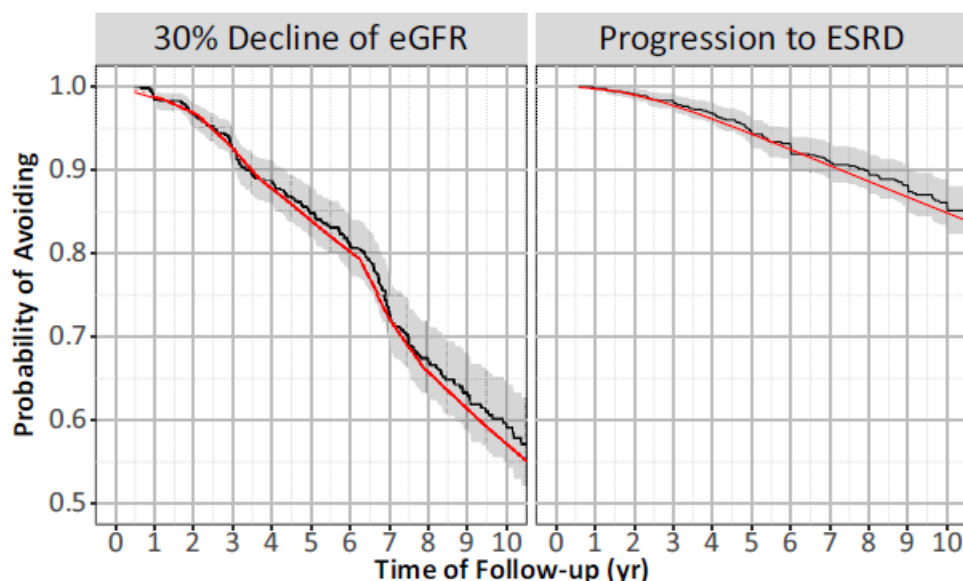


Figure 3.

Model-predicted versus observed probabilities for avoiding a 30% decline of eGFR and ESRD over time. (Adapted from Perrone et al., 2017).

CASE STUDY #2: STREAMLINING CLINICAL DEVELOPMENT

Quantitative methods also include optimal sampling for pharmacokinetics and pharmacodynamics. Quantitative systems pharmacology (QSP) can be applied to aid mechanistic understanding and offer hypothesis generating opportunities in cases where information gaps may limit using more empiric approaches. Where there are challenges in exploring dynamic dose ranges in clinical trials, such quantitative methods can be used to interpolate or extrapolate dose/response. Physiologically-based pharmacokinetic (PBPK) modeling can reduce the number of clinical studies performed in a rare disease program. Bonner et al (2021) developed and verified a PBPK model for the endogenous hormone cortisol (hydrocortisone) in healthy adults, and children and adults with adrenal insufficiency. Such models would be useful tools to predict adult and pediatric pharmacokinetics of hydrocortisone formulations and support clinical dosing regimens.

CASE STUDY #3: USING MIDD TO ASSESS THE IMPACT OF ORGAN IMPAIRMENT

Obeticholic acid (OCA) is a selective and potent farnesoid X receptor (FXR) agonist in development for treating chronic nonviral liver diseases. A physiologic pharmacokinetic model was developed by Edwards and coauthors (2016) to quantitatively describe the absorption, distribution, metabolism, and excretion (ADME) of OCA in patients with and without hepatic impairment (Figure 4). Their results showed that moderate and severe hepatic impairment substantially increased the systemic exposure of OCA, whereas concentrations of OCA in the liver, the primary site of pharmacological activity, only marginally increased. Such physiologic pharmacokinetic models allow selecting meaningful surrogates for hepatic exposure minimizing the number of studies needing to assess the impact of organ impairment.

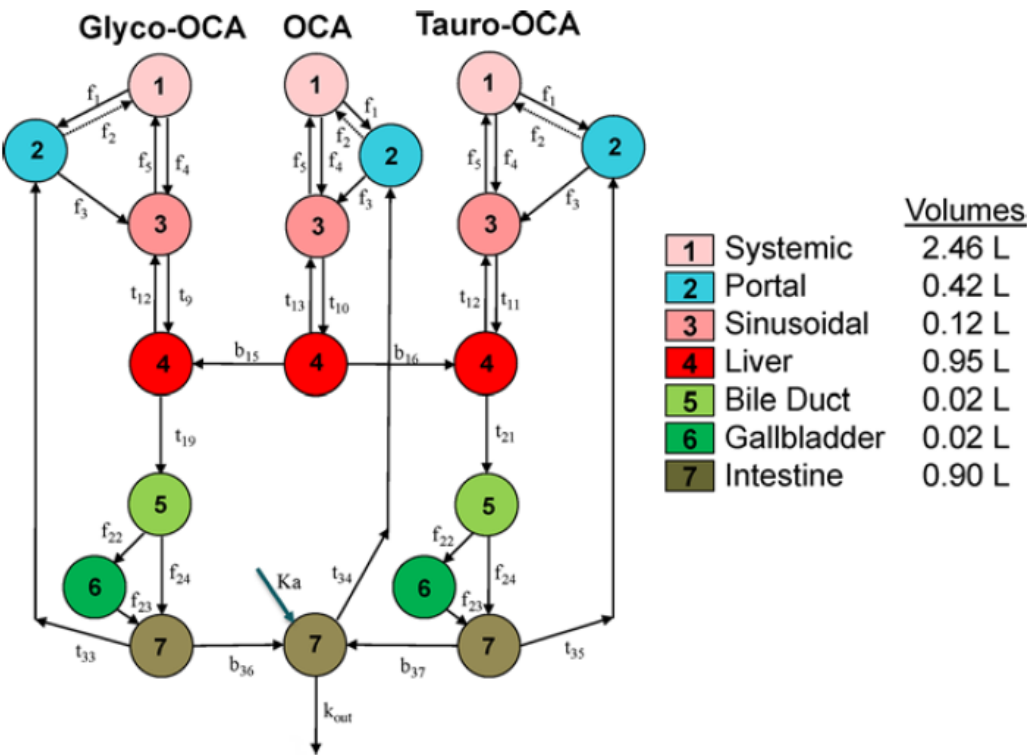


Figure 4.
Physiologic pharmacokinetic model for OCA (Adapted from Edwards et al., 2016)

CASE STUDY #4: USING HEOR TO QUANTIFY BURDEN OF ILLNESS”

Another key area of impact is using external controls as well as health economics outcome research (HEOR), payer value and market access expertise. Take the case of Dravet syndrome (DS), for example. DS is a rare, genetic, life-limiting epilepsy. This syndrome is characterized by frequent and severe convulsive seizures, with an increased risk of death due to sudden unexpected death in epilepsy (SUDEP). The significant burden of caring for patients with DS, arising from high seizure frequency and a wide range of comorbidities, negatively impacts day-to-day quality of life (QoL), for both the patient and the parents. Quite meaningfully, real-world data for patients with DS are non-existent, and the use of patient-reported

outcomes that shows the impact of seizures on QoL is limited. Teneishvili and coworkers (2020) reported on the impact of seizures on the QoL of DS patients. Their work showed that both adjusted univariate and multivariate analyses, a higher monthly seizure frequency was associated with poorer QoL. For every 10 additional seizure episodes suffered, patients experience a significant 13% decrement to their QoL. Their data showed that a range of comorbidities have a profound impact on QoL and highlighted the high unmet medical need for patients with DS to have access to new treatments that reduce seizures and to critically improve QoL for patients and their families.

These vignettes of model-informed drug development examples underscore the value of such applications in rare diseases, whether it is study design, choice of endpoints, or minimizing study burden. Figure 5 summarizes the methods to increase the probability of rare diseases development probability of success.

Figure 5.

Achieving success in rare diseases development using Certara technology-enabled strategic consulting.

Certara helps to overcome the challenges in orphan drug development with model-informed drug development (MIDD)

Small patient pools

- We use clinical pharmacology expertise in combination with MIDD tools to discern effects in small patient populations

Sensitive patient populations

- We model the impact of a new drug on other disease states or untested populations

Unique regulatory landscape

- We provide end-to-end regulatory support and medical writing services: from meetings with Health Authorities to preparation and submission of marketing application

Reimbursement challenges

- We develop a quantitative multicriteria-decision analysis-based framework adapted to the very specific issues in rare disease development and access including quality of evidence, disease severity, ethical considerations, population-level factors, economic impact of the disease, and specific budgetary impact

SUMMARY

Rare diseases encompass a restrictive and poorly accessible patient pool. Moreover, the scarcity of the patient population for clinical trials makes data interpretations quite challenging. While rare diseases drug developers frequently seek accelerated approvals, these present tenuous, often insurmountable, challenges in fully realizing them. That is partly because the natural history of the disease is not well known, and the choice of early biomarkers and surrogate endpoints rarely predict clinical benefit. Many of these limitations can be addressed using a model-informed drug development enabled program, reducing uncertainty in both technical and regulatory success. The effective utilization of the accelerated approval pathway for rare diseases relies on the development and use of a scientifically sound framework of qualifying biomarker endpoints as an acceptable surrogate

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

For more information on our rare disease capabilities, please visit our Rare Disease and Orphan Drug Resource Center (<https://www.certara.com/services/practice-areas/rare-disease-and-orphan-drug-development-resource-center/>).

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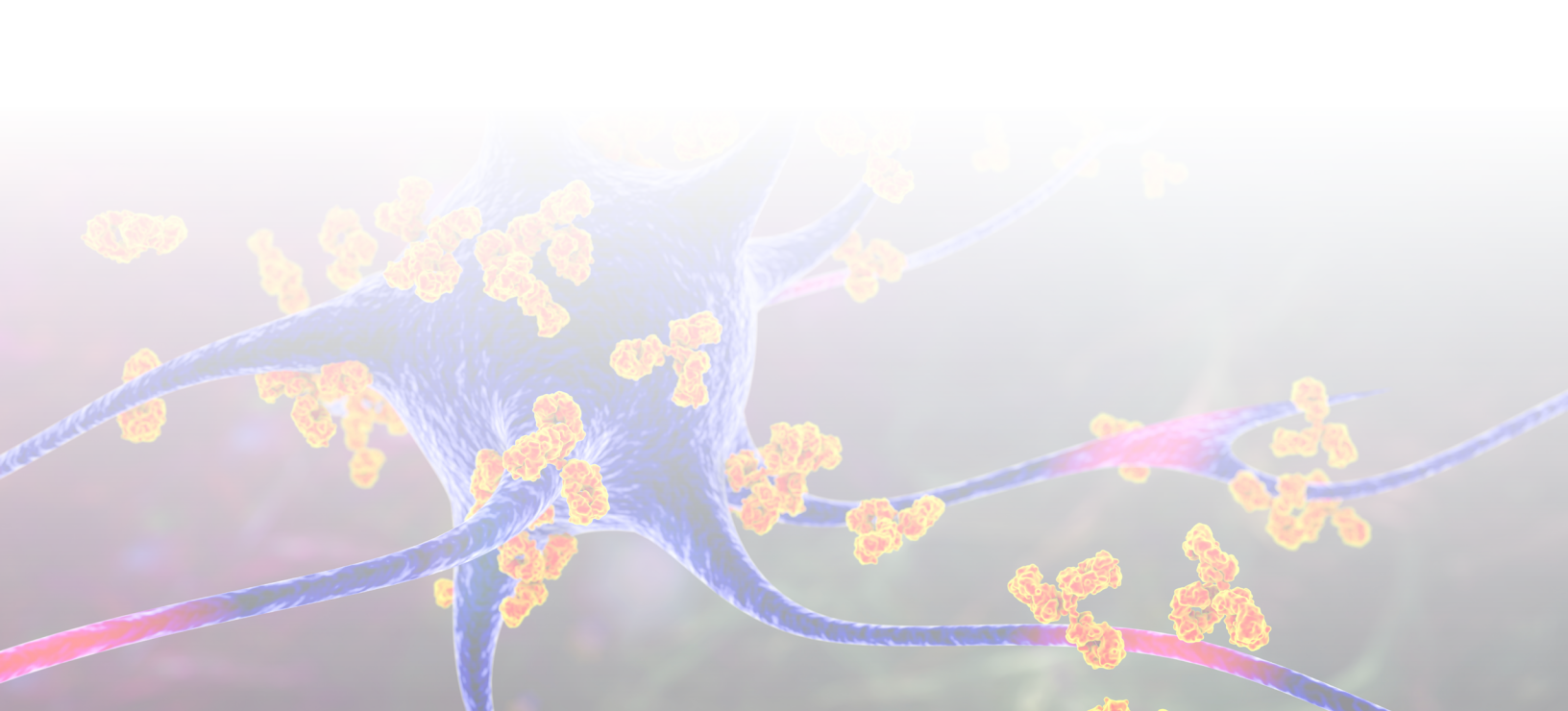
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About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services that transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions and regulatory agencies across 62 countries.

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