

# Rare Disease and Orphan Drug Development

There are 7,000 rare diseases impacting 350 million patients worldwide, yet only 300 of these diseases have approved treatments. This gap, impacting 95% of those suffering from rare diseases, represents a huge unmet medical need.

## Unique Challenges Require Unique Development Approaches

Developing drugs for rare diseases poses a range of clinical, regulatory and commercial challenges. The small number of patient populations impact the ability to identify and recruit for clinical trials. Many orphan diseases are genetically based and oftentimes these patients have complex phenotypes that react very differently to proposed treatment protocols. The diseases may be poorly understood, making it difficult to set clinical endpoints, biomarkers or outcome measures. Patients may also fall into an ethically sensitive population, ranging from neonates and pediatrics to people with co-morbidities.

## Modeling and Simulation Streamline Orphan Drug Development

Modeling and simulation (M&S) approaches are not only ideal for the development of orphan drugs, but are encouraged by regulators. M&S allows us to quantify the drug-disease-trial and exposure-response models from small populations, gaining insight into biomarkers and endpoints. It is used to facilitate dose selection, identify drug-drug and drug-food interactions, recommend the pediatric treatment when only adult data is available, and model the impact of the drug on other disease states.

Increasingly, the regulatory agencies have demonstrated extraordinary flexibility in approving orphan drugs, either through the use of accelerated approval pathways, the elimination of a second pivotal clinical trial, or modeling and simulation in lieu of certain trials. Certara has brought together the technology, experience and expertise to deliver unique scientific leadership to this challenging field, by using that leadership to extract the most amount of knowledge from the (often times) small amount of pre-clinical and clinical data.

## Certara's Full Portfolio of M&S Technologies

Certara's more than 130 PhD scientists and modeling experts use mechanistic, semi-mechanistic and empirical physiologically-based pharmacokinetic (PBPK) and pharmacokinetic/pharmacodynamic (PK/PD) data along with unique computer models to determine the relationship between a drug dose, how it is absorbed and excreted, and how the body responds. They combine data from preclinical studies and first-in-human clinical trials with trial design information from

### Global Rare Disease Regulation

Status of legislation to support rare disease drug development and authorization:

- US – 1983
- Japan – 1993
- Australia – 1998
- EU – 2000
- Korea – 2004
- Thailand – 2007
- Taiwan – 2004
- Canada – proposed
- China – proposed

In addition, many other countries provide expedited review pathways for rare disease therapies.

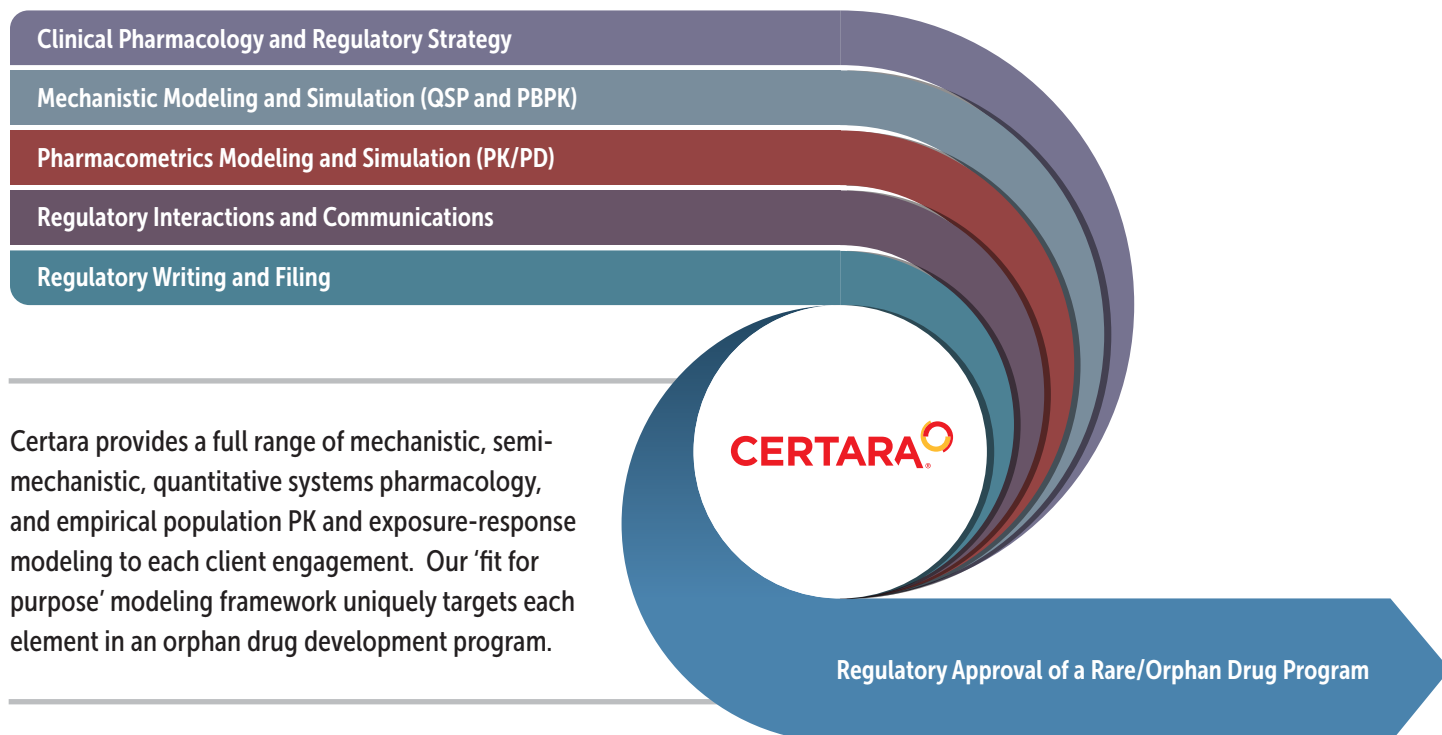
the medical literature. They also use these quantitative methods to test how patients' age, weight and disease state can alter drug exposure and response, and to run "what if" simulations for patient populations that are taking several medications for different conditions. Certara can leverage not only its unparalleled experience in using M&S for rare drug development, but its unique tools, including the Simcyp population-based and pediatric simulators for PBPK analysis, and Certara's Phoenix software for PK/PD analysis.

Certara's unparalleled experience, unique technology and subject-matter expertise are applied to address the distinct challenges associated with rare disease drug development:

- Large heterogeneity in disease progress and treatment outcomes
- Poor understanding of disease progression
- Few patients to run clinical studies
- Uncertain appropriate duration of treatment
- Sparse existing data available from limited populations
- Age and organ maturity variation
- Lack of appropriate endpoints that predict outcomes

### Supporting Regulatory Interactions

As seasoned drug developers, Certara's team of scientists, clinical pharmacologists, regulatory strategists and regulatory writers work alongside orphan drug development teams on global drug approvals. Our Synchrogenix regulatory writing team has more than 100 writers with special proficiency in orphan, pediatric, oncology and global filings, as well as a deep understanding of how to articulate the results derived from M&S.



Certara provides a full range of mechanistic, semi-mechanistic, quantitative systems pharmacology, and empirical population PK and exposure-response modeling to each client engagement. Our 'fit for purpose' modeling framework uniquely targets each element in an orphan drug development program.

Certara has supported the approval of scores of orphan drugs, including nine in 2015 alone.

## Unparalleled Experience in Orphan Drug Development

### Genetic & Hereditary

- Fabry Disease
- Pompe Disease
- Hunter's Disease
- Metachromatic Leukodystrophy Disease
- Transthyretin-mediated Amyloidosis
- Familial Mediterranean Fever
- Urea Cycle Disorder
- Hereditary Angiodema
- ACE-induced HAE
- Lennox-Gastaut Syndrome
- Gaucher Disease
- Cystic Fibrosis
- Hypophosphatasia

### Antinfectives/Antivirals

- Anthrax
- Orthopoxvirus/Smallpox
- Symptomatic Botulism
- Respiratory Syncytial Virus

### Oncology

- Acute Lymphoblastic Leukemia
- Metastatic Myeloma
- Multiple Myeloma
- Acute Myeloid Leukemia
- Urinary Bladder Cancer (Photodynamic Therapy)
- BRAF Mutation
- Blood Cancer
- Ovarian Cancer

### Gastrointestinal

- Short Bowel Syndrome
- Pediatric Crohn's Disease
- Carcinoid Syndrome

### CNS

- Myasthenia Gravis
- Restless Leg Syndrome
- Spasticity due to Multiple Sclerosis
- PKAN (Pantothenate Kinase-associated Neurodegeneration)
- Friedreich's Ataxia

### Bone and Muscle Disease

- X-linked Hypophosphatemia (Vitamin D-resistant Rickets)
- Duchenne Muscular Dystrophy
- Hypophosphatasia

### Blood Disorders

- Paroxysmal Nocturnal Hemoglobinuria
- Atypical Haemolytic Uremic Syndrome (aHUS)
- Beta-thalassemia (Sickle Cell Beta-thalassemia)

### Other

- Radiation Poisoning
- Hypoparathyroidism
- Molybdenum Deficiency
- Hyperuricemia in Patients with Gout Refractory
- Peyronie's Disease

Examples of the rare/orphan disease drug development plans that Certara has supported in recent years



## About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit [www.certara.com](http://www.certara.com) or email [sales@certara.com](mailto:sales@certara.com).