



# Rare Diseases

A Report on Orphan Medicines in the Pipeline

## More Than **700** Medicines in Development Pipeline for Rare Diseases

Rare diseases may have small patient populations, but they are anything but rare. More than 400 million people worldwide are affected by one of the approximately 8,000 rare diseases known to exist today. In the U.S., as many as 30 million people have a rare disease and about 80% of rare diseases are genetic in origin with the vast majority—about 50%—impacting children.<sup>1</sup>

In the U.S., a disease or condition is defined by the U.S. Food and Drug Administration (FDA) as rare—or orphan—when it affects fewer than 200,000 people.<sup>2</sup> Many rare diseases impact significantly smaller groups of patients, sometimes as small as a few hundred or even less.

For people with a rare disease, simply getting a diagnosis can be a complicated, lengthy and frustrating journey. Inadequate diagnostic tools and limited awareness of rare diseases along with available treatment options make it difficult to identify and diagnose rare diseases. On average, it can take more than seven years, and an often-burdensome process, for a rare disease patient to receive an accurate diagnosis.<sup>1</sup>

### JUST THE FACTS

**30 million**

Americans—nearly 1 in 10—  
have a rare disease<sup>1</sup>

**8,000**

estimated number of rare  
diseases worldwide<sup>1</sup>

More than

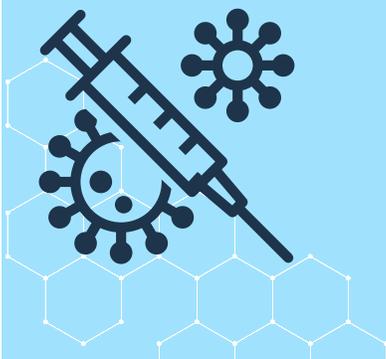
**600**

medicines approved in the U.S.  
for rare diseases<sup>2</sup>

Less than

**10%**

of rare diseases have an  
approved treatment<sup>3</sup>



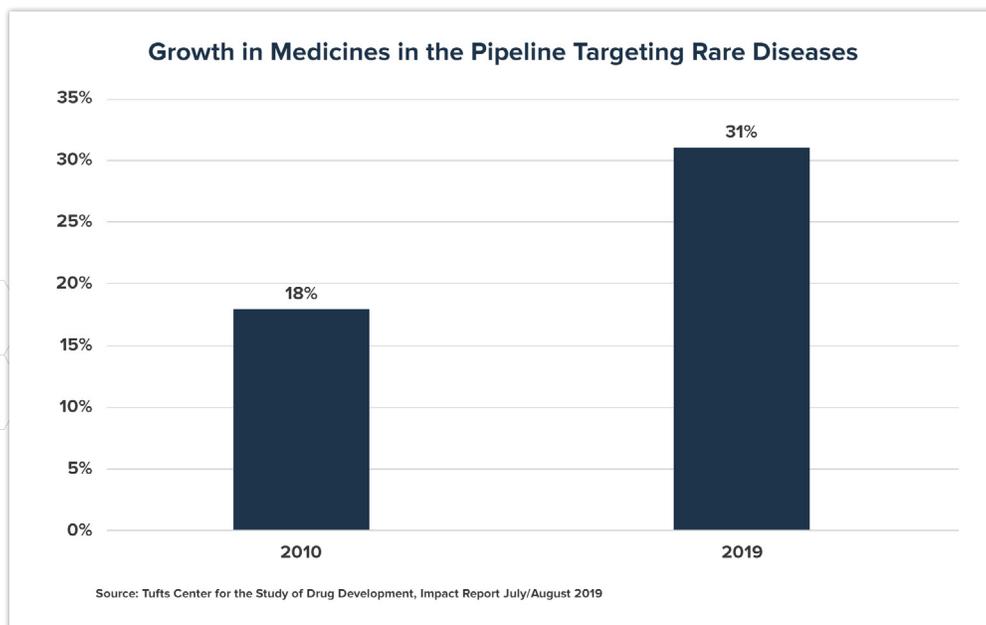
In addition to diagnostic challenges facing rare disease patients, developing medicines to treat them is particularly challenging due to the complexity of the diseases themselves. Owing to these challenges, from clinical development through approval, rare disease drug development takes on average four years longer than those for non-rare diseases.<sup>4</sup>

Despite the many difficulties associated with rare disease drug development, researchers have made tremendous progress in the development of medicines to treat rare diseases over the past 30 years—including new treatments for many genetic disorders and rare forms of cancer. Unfortunately, today less than 10% of rare disease currently have an FDA-approved treatment option. The medicines in development today represent the continued commitment of biopharmaceutical companies to meet this significant unmet medical need and to overcome the challenges inherent in developing medicines for rare diseases.



## Challenges in Developing Treatments for Rare Diseases

America's biopharmaceutical companies are leveraging new technologies and expanding scientific understanding of the genetic basis of many rare diseases to develop groundbreaking therapies for them. Advances in personalized medicine and cell and gene therapies are among some of the innovative approaches that are creating new opportunities to advance research into rare diseases and the development of new treatments. Due in part to biopharmaceutical research and development (R&D) becoming increasingly focused on genetic factors, 31% of medicines in the pipeline target rare diseases, up from 18% in 2010.<sup>4</sup> But with these opportunities come unique challenges, including high rates of failure given research into diseases and conditions for which little is known.



The development of new and effective treatments for rare diseases faces many challenges including:

### *Overcoming the Scientific Knowledge Gap*

The complex biology, heterogeneity and progressive nature of many rare diseases present unique hurdles for scientists. There remain significant gaps in medical and scientific understanding of the underlying causes of many of these conditions, particularly as the natural history or the progression of many of these diseases has yet to be fully understood. At the same time, even within a particular disease, there can be many subtypes or variations resulting in different clinical manifestations and disease courses. It is vital that researchers overcome the gap in understanding the biology of individual rare diseases and accelerate the development of treatments and even potential cures for the many patients impacted by them.

### *Complexities of Rare Disease Drug Development*

Rare diseases, particularly where there are no available treatments, pose unique scientific and regulatory challenges. From a scientific perspective, while some rare diseases have been named and characterized over time, researchers may not have identified the cause or they may have identified multiple potential causes of disease. Knowing the cause of the disease also doesn't necessarily mean that researchers understand the mechanism of disease. Other challenges include identifying, or sometimes developing, biomarkers and animal models, selecting between multiple and complex biological pathways for study, and working with few well-developed clinical trial endpoints and outcome measures.

It is often difficult to design and recruit patients for rare disease clinical trials due to small patient population size, differing patient presentation because of genetic variations and timing of symptoms and widely geographically dispersed patient populations (in some cases there may be a few hundred patients or fewer around the world). Moreover, rare diseases often disproportionately impact pediatric populations, which present their own unique challenges in clinical trial recruitment and development. For extremely rare diseases or conditions, patients may have to travel long distances to consult with health care providers who have experience in the study or treatment of their rare diseases. Clinical trials for rare diseases overall engage more investigative clinical trial sites to recruit fewer patients, reflecting difficulties of patient identification and enrollment.<sup>4</sup>



## **Progress in Rare Disease Research & Development**

Recognizing the scarcity of medicines to treat diseases with small patient populations and the uncertain road researchers face in pursuing such challenging disease areas, the Orphan Drug Act (ODA) of 1983 introduced important incentives for companies to develop rare disease treatments.

The ODA, as currently amended, provides sponsors of approved orphan drugs with seven years of exclusivity, meaning that FDA cannot approve the same drug for the same orphan use for seven years following approval. The ODA also provides an R&D tax credit for 25% of qualified clinical trial costs for orphan drugs.<sup>5</sup> In addition, federal funding is available through grants to perform clinical trials of orphan products, which is particularly critical for small and emerging companies.

The ODA has been regarded as a tremendous success, with more than 600 medicines approved for rare diseases since its passage, compared to fewer than 10 between 1973 and 1983.<sup>2</sup> Despite the tremendous progress that has been made since the passage of the ODA, more than 90% of known rare diseases still do not have an FDA-approved treatment option.

Despite the above challenges, biopharmaceutical researchers have leveraged new technologies and the growing scientific understanding of many rare diseases, to develop groundbreaking therapies for some rare diseases. In 2020, more than half (55%) of novel new drug and biological approvals were orphan drugs for rare diseases.<sup>6</sup> In 2020, medicines approved to treat orphan disease included a drug targeting von Hippel-Landau disease, a genetic disease that causes tumors and/or cysts to grow in different parts of the body and affects 10,000 people in the U.S.<sup>3</sup> Additionally, medicines were approved to reduce the risk of molybdenum cofactor deficiency type A, a genetic disease characterized by brain dysfunction and severe development delay in children affecting 1 in 200,000 births worldwide,<sup>7</sup> and plasminogen deficiency type 1, a rare disease causing inflamed growths on mucous membranes affecting about 1.6 people per 1 million worldwide.<sup>3</sup>

Some recent medicine approvals provide treatment options for patients where there were few or none previously available include:

- The first oral medicine for spinal muscular atrophy (SMA), a rare and often fatal genetic disease affecting muscle strength and movement, to treat patients two months of age and older.
- The second enzyme replacement therapy approved for children as young as 1 year to treat late-onset Pompe disease, a rare genetic disease that can cause the accumulation of glycogen (a complex sugar) in the skeletal and heart muscles leading to premature death.

## The Rare Disease Pipeline

Today, biopharmaceutical research companies are continuing that progress with 791 medicines<sup>8</sup> in development for a broad range of rare diseases. There is hope on the horizon as scientists are uncovering more about rare diseases at the molecular and genetic levels which is driving the development of innovative treatments for rare diseases. The 791 medicines in development, all in clinical trials or awaiting review by the FDA, include:

- **168** for rare cancers and **120** for rare blood cancers, which together account for 35% of the 791 rare disease medicines in development.
- **192** for genetic disorders, including cystic fibrosis and spinal muscular atrophy (SMA).
- **56** for neurological disorders, including amyotrophic lateral sclerosis (ALS) and seizures.
- **54** for blood disorders, including sickle cell disease and hemophilia.
- **51** for autoimmune diseases, including systemic sclerosis and juvenile arthritis.
- **36** for infectious diseases, including rare bacterial infections and hepatitis.

Other medicines in development target treatments for patients living with Cushing's syndrome, polycystic ovary syndrome, systemic light chain amyloidosis, graft versus host disease, acute radiation syndrome and primary sclerosing cholangitis, among others.

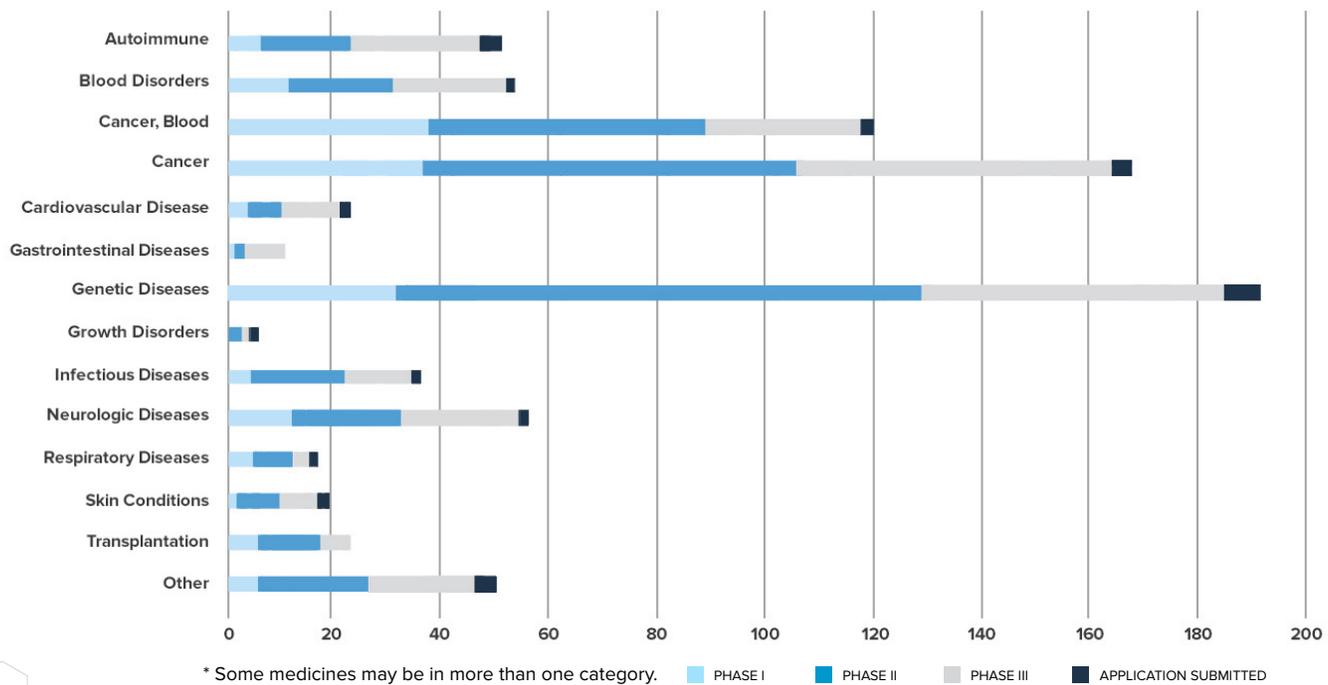


## Select Medicines in Development for Rare Diseases Utilizing Innovative Approaches

Among the 791 medicines in development for more than 300 rare diseases are treatments that employ scientific and technical knowledge in new ways or expand on current knowledge. Many of the medicines represent innovative new ways to target a rare disease, including:

- A potential first-in-class medicine is in development for the treatment of **obstructive hypertrophic cardiomyopathy (HCM)**, a chronic heart condition with high death rates and difficult symptoms for patients. HCM is most often caused by abnormal genes in the heart muscle. These genes cause the walls of the heart chamber (left ventricle) to contract harder and become thicker than normal. In obstructive HCM, the wall between the two bottom chambers of the heart thickens. The thickened walls become stiff reducing the amount of blood taken in and pumped out to the body with each heartbeat. The medicine in development is a cardiac myosin inhibitor designed to reduce left ventricular contraction by modulating the function of cardiac myosin, the protein that drives heart muscle contraction.
- A potential first-in-class medicine is being developed to treat **systemic lupus erythematosus (SLE)**, an autoimmune disease with limited treatment options. In SLE, the immune system attacks its own tissues, causing widespread inflammation and tissue damage in organs, such as the joints, skin, brain, lungs, kidneys and blood vessels. The potential treatment is a dual inhibitor of the CD28 and inducible T-cell co-stimulator protein (ICOS) costimulatory pathways. It works by simultaneously blocking the two pathways to reduce T- and B-cell immune responses that play a key role in several autoimmune and inflammatory diseases.
- A long-acting recombinant human growth hormone is being developed as treatment for both pediatric and adult **growth hormone deficiency**. Growth hormone deficiency occurs when the pituitary gland doesn't produce enough growth hormone to stimulate the body to grow. Because of the treatment's long-acting properties, it has the potential to be a once-weekly injection compared to the current standard of daily injections, improving compliance and treatment outcomes.
- An antisense treatment in development for **amyotrophic lateral sclerosis (ALS)** is thought to reduce the production of mutated superoxide dismutase (SOD1) protein and potentially the fatal progression of SOD1-ALS. This mutated protein has been associated with the degeneration of motor neurons in ALS. SOD1-ALS is a rare form of the disease that accounts for 20% of inherited or familial ALS and 2% of all ALS cases.<sup>9</sup>
- A medicine approved to treat eosinophilic asthma is being further developed for the rare diseases of **eosinophilic granulomatosis with polyangiitis, eosinophilic esophagitis and hypereosinophilic syndrome**. These conditions are caused by a high level of eosinophils (a type of white blood cell that helps fight infection) and inflammation of small to medium sized blood vessels which can affect various organ systems including the lungs, gastrointestinal tract, skin, heart and nervous system. The potential medicine is a monoclonal antibody that recruits natural killer cells to induce direct, rapid and near-complete depletion of eosinophils.
- A potential first-in-class treatment is in development for **alpha-1 antitrypsin-associated liver disease (AATLD)**, a rare genetic disease that can lead to fibrosis, cirrhosis and an increased risk of liver cancer. The treatment is a subcutaneously administered RNA interference (RNAi) therapeutic that inhibits the production of mutant alpha-1 antitrypsin proteins, the cause of progressive liver disease in AATLD patients.
- An investigational bio-engineered adeno-associated virus (AAV) vector-based gene therapy is being developed to treat **hemophilia A**, or factor VIII deficiency. Hemophilia is a rare, serious inherited hematologic disorder, characterized by mutations in the F8 gene. The mutation leads to deficient blood coagulation and an increased risk of bleeding or hemorrhaging.

## Medicines in Development for Rare Diseases\*



## Accelerated Approval: How It Helps Rare Disease Patients<sup>10</sup>

The accelerated approval pathway, formally established by FDA regulations in 1992 and later codified in statute in 1997, enables expedited access to medicines that address an unmet medical need for serious and life-threatening diseases and conditions, while preserving FDA’s high standards for safety and effectiveness. This pathway has provided timely access to treatments to patients living with HIV/AIDS, numerous rare cancers and other rare diseases and conditions, leading to earlier access to potentially life-saving therapies and better health outcomes for millions of patients.

Importantly, a medicine approved via the accelerated approval pathway must meet the same FDA standards for safety and efficacy to obtain approval as other medicines. However, as opposed to utilizing a direct measure of clinical benefit, the FDA can base an accelerated approval upon a measure of an accepted surrogate endpoint—a marker such as a laboratory measurement, radiographic image, physical sign, or other measure—or an intermediate clinical endpoint such as a symptom relief, that is reasonably likely to predict clinical benefit. For example, in clinical trials for cancer, where most accelerated approvals are granted, researchers may be able to detect a medicine is having an effect on tumor growth before demonstrating an effect on survival or morbidity, which generally requires long, large trials because of the duration of the typical disease course. In this case, the reduction in tumor growth would be the “surrogate endpoint” that is reasonably likely to predict clinical benefit. Additionally, shorter lengths of time than would be required from having to use overall survival as the specific measure of clinical benefit, both of which are significant barriers to orphan drug development in cancer.

When deciding whether a medicine should be approved via the accelerated approval pathway, the FDA carefully considers the scientific data behind the surrogate endpoint proposed and requires substantial evidence of effectiveness for approval, maintaining the same gold standard review process and requirements for safety and effectiveness as for other FDA-approved medicines.

The FDA requires sponsors of accelerated approval products to conduct post-approval studies to verify the anticipated clinical benefit. The Agency also has expedited procedures to withdraw a product or indication approved under the accelerated approval pathway based on a number of reasons, including if the post-approval studies fail to verify the predicted benefit.

The accelerated approval pathway has provided patients with access to therapies faster than FDA's traditional pathway. Since inception, over 250 new drugs and biologics to treat serious or life-threatening illnesses have been approved through accelerated approval, including 165 in the past decade. Some recent examples of rare disease approvals under the FDA's accelerated approval pathway include:

- The first targeted treatment for adults with non-small cell lung cancer (NSCLC) that has spread to other parts of the body with a specific KRAS mutation, as determined by an FDA-approved diagnostic test, for whom at least one other therapy was not successful. KRAS mutations account for about 25% of mutations in NSCLC. Accelerated approval was based on the objective response rate (proportion of patients whose tumor is destroyed or reduced) and duration of response.<sup>11</sup>
- The first treatment for Duchenne muscular dystrophy (DMD) in patients who have a specific mutation of the DMD gene. About 8% of patients with DMD have this mutation. Accelerated approval was based on an increase in dystrophin (a protein that helps keep muscle cells intact) production in skeletal muscle observed in patients treated with the therapy.<sup>12</sup>
- An oral, once-daily medicine for the treatment of metastatic NSCLC with a certain mesenchymal-epithelial transition (MET) mutation. The mutation occurs in about 3%-4% of NSCLC cases and is an aggressive cancer associated with poor outcomes. Accelerated approval was based on overall response rate and duration of response.<sup>13</sup>
- A medicine for the treatment of light chain amyloidosis, a blood cell disease that causes thickening and failure of vital organs, in combination with other therapeutics for newly-diagnosed patients through injection as opposed to IV administration. Approximately 4,500 people develop this disease each year in the U.S. Accelerated approval was based on the hematologic complete response rate (hemCR) measure.<sup>14</sup>
- The first treatment of Chagas disease, a parasitic infection spread by “kissing bugs” that can lead to congestive heart failure, in pediatric patients from birth to less than 18 years of age. Accelerated approval was based on a portion from the phase 3 program.<sup>15</sup>

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