Meeting the Need: Rare Diseases and the Orphan Drug Act

Overview

- Characteristics of Rare Diseases
- Progress Against Rare Disease
- Challenges in Orphan R&D
- The Orphan Drug Act
- Orphan Drug Market Dynamics
- Fostering Continued Innovation in Rare Diseases

Characteristics of Rare Diseases

In the United States, Rare Disease is Defined as a Disease or Condition That Affects Fewer Than 200,000 People

Approximately **7,000** different rare diseases are known today, with many more still to be identified

Examples of rare diseases include:

Amyotrophic Lateral Sclerosis (ALS)

Sickle Cell Anemia

Cystic Fibrosis

Many Types of Cancer

Source: Global Genes

Taken Together, Rare Diseases Are Not That Rare

Although most rare diseases impact fewer than 10,000 people, their impact on public health is far-reaching. In total, rare diseases affect 30 million Americans.

RARE DISEASES AFFECT **30 MILLION AMERICANS**

THAT'S 1 IN 10

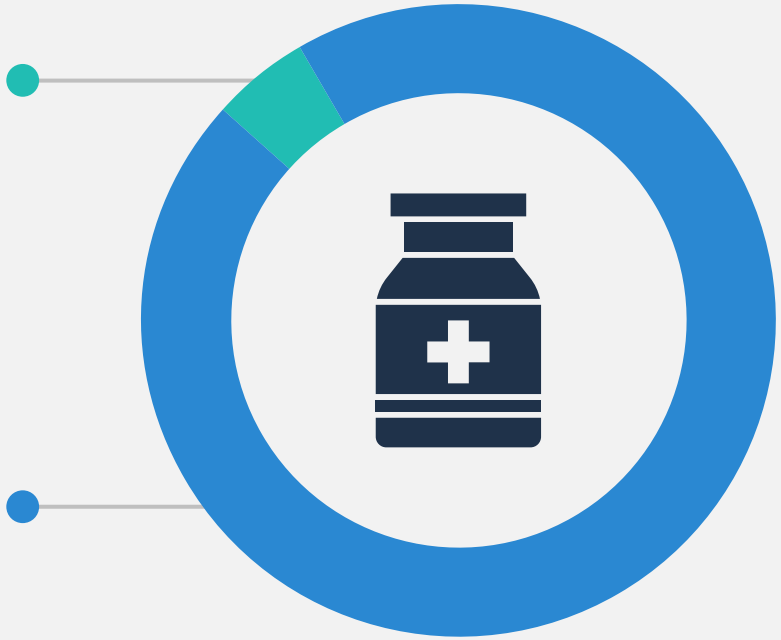
Sources: National Human Genome Research Institute, Braun M et al., Global Genes

Treatment Options for Rare Diseases are Limited and Represent a Significant Unmet Need for Patients

Only 5% of all rare diseases have an FDA-approved treatment option.

Rare diseases **WITH** FDA approved medicine
5%

Rare diseases **WITHOUT** FDA approved medicine
95%



85% to 90%
of rare diseases are considered “serious or life threatening.”

Sources: GAO, FDA, Global Genes

Across rare diseases, individuals and families have unique challenges they must manage daily

Obtaining a Diagnosis

- The inherent nature and complexities of rare diseases may mean that an accurate diagnosis can take more than seven years after the onset of symptoms

Complexity of Care

- Rare diseases often damage many organs and body systems
- Multisystem impacts require numerous specialists to manage different aspects of their condition
- Rare disease patients often have to manage complicated care schedules and medication regimens
- Logistical challenges related to accessing the often geographically dispersed specialists impacting patient quality of life and productivity
- Logistical challenges and complexity of care can result in significant impact on caregivers and families

Emotional and Psychological Stress

- Rare diseases take a measurable toll on the emotional and psychological well-being of both patients, their families, and care givers
- Patients can experience feelings of isolation, depression, stress and other issues related to managing their condition impacting quality of life

The Need for Medical Advances Reflected by Costs for Rare Associated with Diseases with No or Limited Treatment Options

Amyotrophic Lateral Sclerosis (ALS)

Nervous system disease that weakens muscles and impacts physical function

- An ALS patient's direct medical costs total over $1.4 million over the course of the disease, including in-home caregiving and hospital care
- This does not include non-medical expenses and lost income

Sickle Cell Disease (SCD)

A group of disorders that cause red blood cells to become misshapen and break down

- For an average person with SCD reaching age 45, total lifetime health care costs were estimated to be nearly $1 million, with annual medical costs ranging from over $10,000 for children to over $30,000 for adults

Scleroderma

An autoimmune disease of the connective tissue

- Adjusted annual direct and indirect costs of scleroderma in the United States have been estimated at $2.3 billion
- It has been estimated that patients lose $300,000 in lifetime earnings because of their condition

Sources: Resnick, Chodorow and Associates; Obermann & Lyon, American Society of Hematology

Progress Against Rare Diseases

Medicines Are Transforming Treatment For Many Rare Diseases

Although great unmet need remains, we have seen remarkable progress in the fight against rare diseases over the past decade, providing treatment options to patients for the first time.

SICKLE CELL DISEASE

The first treatment in 20 years was approved in 2017 to treat this inherited blood disorder which can cause severe pain and organ damage. The medicine was approved to reduce complications associated with the disease.

Affects 70,000-80,000 Americans.

BATTEN DISEASE

The first treatment for a form of this severe neurodegenerative disease, was approved in 2017. The medicine is an enzyme replacement therapy approved to slow the loss of walking ability in symptomatic patients 3 years and older.

Affects 2-4 out of every 100,000 US children.

"SLY SYNDROME" (MPS VII)

The first ever treatment for this progressive metabolic condition was approved in 2017. MPS VIII can result in skeletal and organ abnormalities and airway obstruction, leading to reduced life expectancy.

Affects fewer than 150 patients worldwide.

CYSTIC FIBROSIS (CF)

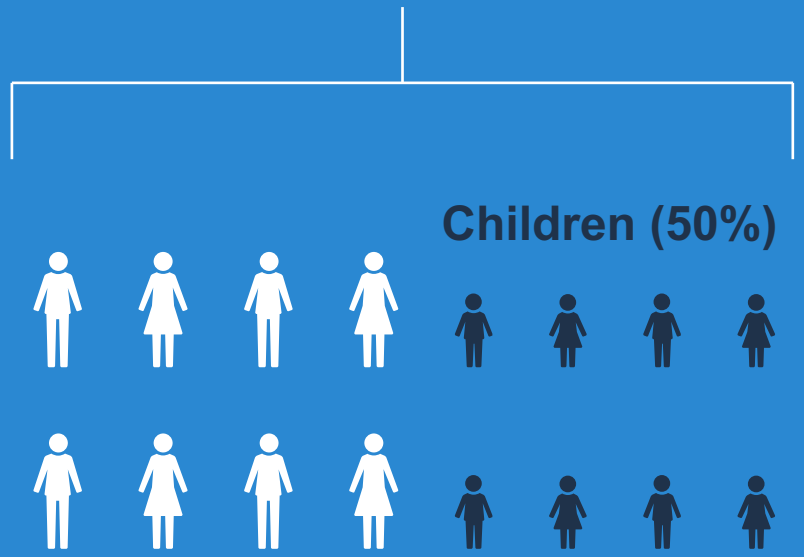
In 2012, FDA approved the first medicine to treat the underlying disease for a subset of CF patients. Since then the drug has been approved for additional CF mutations. CF damages the lungs and digestive system.

Affects 1 in 3,400 US births.

Sources: FDA, Mayo Clinic, NLM, NINDS, NORD, Cystic Fibrosis Foundation

Rare Diseases Disproportionately Impact Children, but Recent Progress Has Improved the Outlook for Many Conditions

Rare Disease Population



Source: Global Genes 2018

Recent Advances in Rare Diseases Impacting Children

Cystic Fibrosis: Genetic disease causing persistent lung infection and other symptoms. Most of the 1,000 new cases each year are diagnosed by the age of 2. New treatments for cystic fibrosis, such as cystic fibrosis transmembrane conductance regulator (CFTR) modulators, can treat the underlying mutations causing the disease.

Mucopolysaccharidosis type 1: Rare lysosomal storage disorder leading to skeletal deformities and delay in motor and brain development, beginning 6-8 months after birth. Enzyme replacement therapy treatments can help manage severe symptoms and promising new therapies are in development.

Ewing Sarcoma: Rare bone tumor that occurs most frequently in adolescents 10 to 20 years of age. Promising treatments such as targeted therapies and immunotherapy are being studied and developed.

Sources: FDA, Global Genes, CFF, NLM, NORD

Advances Over the Past Decade Have Provided More Effective Treatment Options for Managing Hereditary Angioedema (HAE)

HAE is a rare and potentially life-threatening inherited genetic disorder that causes edema (swelling) of the hands, feet, face, airways and gastrointestinal tract, impacting the body's ability to regulate certain biological functions.

State of Care in 2005

- Scientists had little knowledge of the underlying cause of HAE.
- No medications were approved in the U.S. specifically to treat HAE.
- Patients with HAE had limited options to relieve symptoms of an attack, and often were required to undergo invasive procedures to alleviate dangerous swelling.

State of Care Today

- New discoveries in the underlying cause of HAE led to breakthroughs in both preventative and acute treatment options for patients.
- Several medications have been approved by the FDA to treat HAE by targeting the source of the disease.
- Patients are able to self-administer new injectable medications at home to halt acute HAE attacks.

Source: PhRMA

There Have Been Remarkable Advances in the Treatment of Rare Cancers, Including for Chronic Lymphocytic Leukemia (CLL)

CLL is a type of blood and bone marrow cancer that results in a compromised immune system for patients. It progresses slowly and usually affects older adults.

State of Care in 2005

Chemotherapy was the predominant first-line treatment for patients with CLL.

CLL patients already have very weak immune systems, making it sometimes difficult to tolerate chemotherapeutic regimens that may weaken the immune system further.

State of Care Today

The use of novel B-cell receptor (BCR) pathway inhibitors and targeted monoclonal antibodies like rituximab is expanding treatment options for all patients, even those with more compromised immune systems.

New targeted therapies seek to treat the root cause of the disease, resulting in lasting remissions for many CLL patients and without the immunosuppression risks common with chemotherapy.

Source: PhRMA

Orphan Medicines Bring Tremendous Value to the Health Care System – Pulmonary Arterial Hypertension

A study on pulmonary arterial hypertension (PAH) showed that patients taking a new therapy experienced a reduction in costly hospitalizations.

50%
Reduction in PAH-related hospitalizations

52%
Reduction in length of PAH-related hospital stay

Pulmonary arterial hypertension (PAH) is type of high blood pressure that affects arteries in the lungs and in the heart. The condition causes shortness of breath, dizziness, and chest pressure. Over time, the increased blood pressure can damage the heart.

Sources: Channick, R., et al., American Lung Association

Orphan Medicines Bring Tremendous Value to the Health Care System – Infant Botulism

A medicine for infant botulism reduces hospitalization length and cost.

54% reduction
In mean length of hospital stay

$88,600 reduction
In hospital charges per patient

Infant botulism is an infectious intestinal disease caused by ingested bacteria that interferes with the normal interaction between muscles and nerves in infants, resulting in weakness, loss of muscle tone and other severe neurological symptoms.

Sources: New England Journal of Medicine

Venture Capital (VC) Investment in Rare Diseases is Helping Support Medical Innovations

VC investment in rare diseases has **INCREASED SIGNIFICANTLY** over the last decade in both dollars raised and number of companies funded.

$5.8 billion

VC funding for active private and small-cap public companies developing rare diseases treatments in 2017

We believe that by creating a collaborative approach… we [OrbiMed] will generate novel breakthroughs. We can provide greater attention and speed, accelerating the process and moving science to medicine, from the lab to the patient, more rapidly.

VENTURE CAPITALIST & PARKINSON'S DISEASE PATIENT JONATHAN SILVERSTEIN
OrbiMed

Source: BIO, Silverstein, J.

Challenges in Orphan Drug Development

Unique Challenges Exist in Orphan Drug Development

Disease-Diagnosis

- Prevalence of rare diseases is often heterogeneous and variable around the world, e.g., genetic disorders often characterized by wide range of severity, clinical presentation and rate of progression
- Diagnosis challenges:
  - Underdiagnosis and misdiagnosis is frequent due to lack of diagnostic tools
  - Often years between presentation and diagnosis
- Natural histories incompletely described

Patient Populations

- Identifying diagnosed/eligible patients is challenging
- Geographically dispersed and small patient populations make recruiting for and conducting clinical studies difficult
- Given small populations, limited opportunity for study and replication in clinical trials – Few treating physicians, few treatment centers
- Phase 1 clinical trials for rare diseases, on average, engaged six times the number of investigative sites to recruit a quarter of the number of patients, compared to non-rare.

Outcomes Measures

- Lack of outcome measures and clinical endpoints to show impact of new medicines.
- Many rare diseases affect pediatric patients raising additional considerations.

Source: Tufts Center for the Study of Drug Development; FDA

Orphan Drugs Take Longer to Develop Than Other Medicines on Average

As of August 2019, overall development for orphan drugs takes nearly 4 years longer than non-orphan medicines.

Overall development duration (IND – Approval decision), 2014-2018

"In addition to long study start-up and enrollment periods, screen and randomization failure rates are much higher in studies among rare disease patients.

KEN GETZ
Tufts CSDD

Source: Tufts Center for the Study of Drug Development

There is High Uncertainty Associated with Orphan Drug Development

While rare diseases now account for 31% of the R&D pipeline (up from 18% in 2010), the success rate for orphan drugs in clinical trials is estimated to be **only 6%.**

Unsuccessful orphan drugs in development = **94%**

> The clinical development of orphan drugs is fraught with practical challenges. There may be disease-specific complexities, such as poor understanding of natural history of the therapeutic indication due to there being little information available about disease progression, variable phenotypic characteristics of the patient populations and clinical courses, geographical dispersion of a small number of patients and the relative paucity of published clinical trials to inform study execution.
>
> **DR. LINCOLN TSANG**
> ***Partner, Arnold & Porter***

Sources: Pharmaprojects and CH Wong and AW Lo and L Tsang and Tufts

The Orphan Drug Act

The Orphan Drug Act (ODA) Was Passed in 1983 to Support the Development of Medicines for Rare Diseases

Recognizing the unique challenges of developing medicines for patients with rare diseases, Congress passed the ODA to provide incentives for orphan drug research.

The Congress finds that…it is in the public interest to provide such changes and incentives for the development of orphan drugs.

Congressional Findings for the Orphan Drug Act

"Over the past century, the United States—largely through innovative pioneering by private industry and medical researchers in universities—has led the world in developing new drugs that have saved millions of lives. That is a gift to mankind we can be very proud of. Yet the sad fact remains that many diseases still cripple or kill hundreds of thousands of Americans… because no drugs have yet been developed…The bill that I am signing today helps to cure that problem and consequently, we hope, some of the diseases as well."

PRESIDENT RONALD REAGAN, 1983

Sources: Indivisible, FDA

The ODA Provides Targeted Incentives for Biopharmaceutical Innovators to Tackle Rare Diseases

CLINICAL RESEARCH GRANTS:
FDA-administered grants to support orphan drug development. $200K-$400K/year

PDUFA FEES WAIVED:
Exemption from PDUFA fees – unless the application also includes a non-orphan indication.

ODA Incentives

TAX CREDIT:
Tax credit equal to 25% of qualified clinical research costs for new orphan drugs.

SEVEN-YEAR MARKET EXCLUSIVITY:
Precludes approval of the “same drug” for the designated orphan indication only.

Sources: FDA, Office of the Federal Register, FDA

The ODA Has Supported the Development of Hundreds of New Treatment Options for Patients Living with Rare Diseases

“

The Orphan Drug Act has been extremely successful, encouraging research and development of products for diseases that would otherwise have no treatment.

NATIONAL ORGANIZATION FOR RARE DISORDERS

BEFORE ODA

In the decade before the ODA was passed,

ONLY 10 DRUGS

for rare diseases were brought to market

AFTER ODA

Since the passage of the ODA,

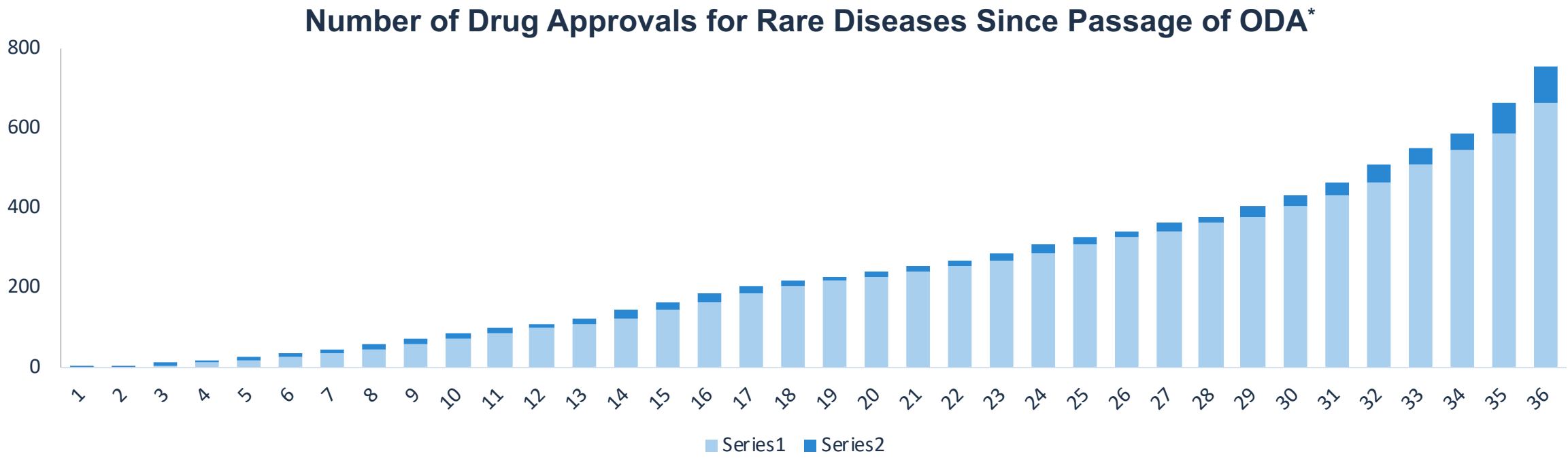
OVER 770 ORPHAN APPROVALS

have been granted, bringing treatments and cures to rare disease patients in need

Sources: FDA, Murphy SM et al., NORD, IOM

The ODA Has Been Instrumental in Bringing New Orphan Approvals to Patients, Yet Great Unmet Need Remains

More than 770 orphan drugs have been approved since passage of the Orphan Drug Act in 1983. However, great unmet need remains.



*Drug approvals for rare diseases include initial approvals of new medicines and subsequent approvals of existing medicines.

Sources: FDA, NIH

The ODA is Critical to Fostering Rare Disease Drug Development

- The ODA provides **narrow but predictable** protection through the 7-year market exclusivity applied to the orphan indication only.
- It has inspired similar legislation in Japan, Australia and Europe

Enacting the Orphan Drug Act in 1983 with its financial incentives and other inducements was an important start to enabling more investment and development of treatments targeted to rare diseases.

SCOTT GOTTLIEB
Then-FDA Commissioner, Feb 2018

Biotechnology as an industry was propelled into a major expansion by the Orphan Drug Act. Thousands of scientific, commercial, and humanitarian opportunities were made possible by the act that could otherwise not have existed.

NATIONAL ACADEMY OF MEDICINE

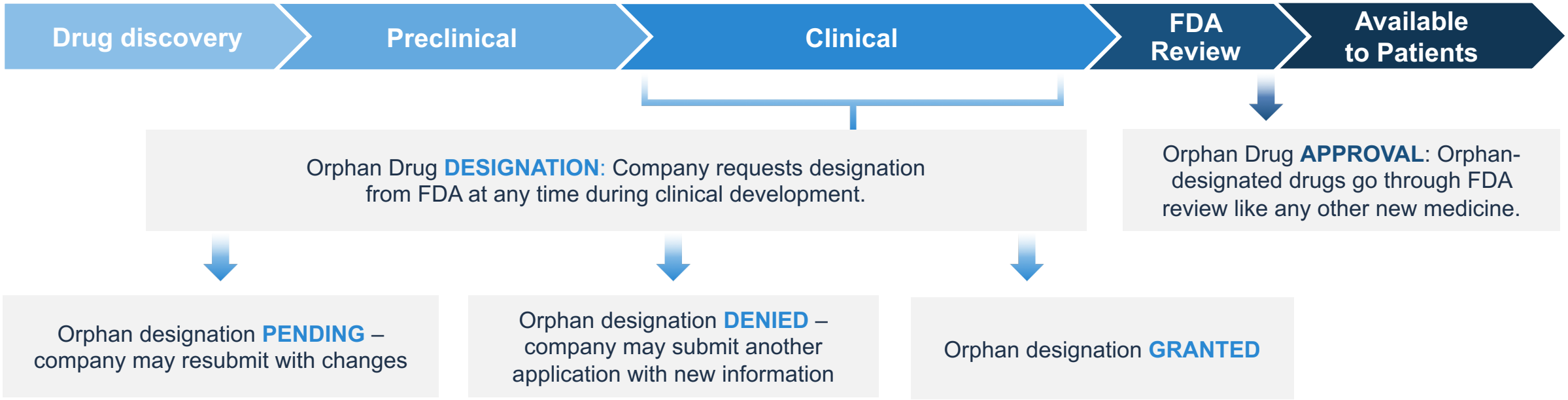
From the patient perspective, the Orphan Drug Act has been extremely successful, encouraging research and development of products for diseases that would otherwise have no treatment.

NORD
Oct 2017

Sources: NORD, FDA, National Academies

The Orphan Drug Designation and Approval Process

To obtain ODA incentives, drug manufacturers submit an application to FDA for orphan designation. Separate from orphan designation, FDA also assess the safety and efficacy of the investigational medicine as it does for all medicines.



Source: GAO

Orphan Designation Requires Extensive Scientific Rationale

- Designations are reviewed by FDA's **Office of Orphan Products Development**
- To receive orphan designation, sponsors must provide **evidence that their potential medicine would treat a disease affecting fewer than 200,000 people**.

Orphan Subsets

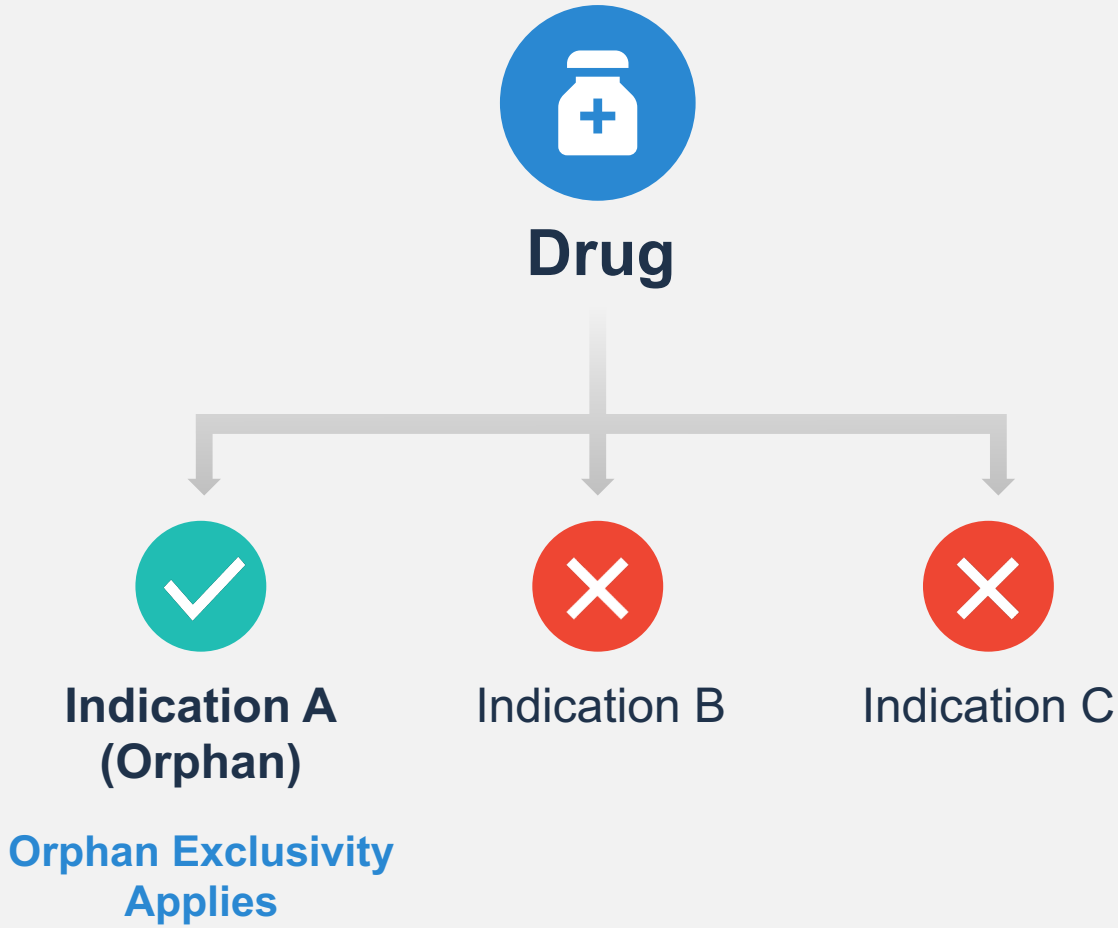
If the population is a subset of a non-rare disease, sponsors must **also** provide evidence that there is reason to believe their potential medicine should be used **ONLY in a given subset** and not in the broader population **due to certain characteristics of the drug** (such as toxicity, mechanism of action, previous clinical experience with the drug, etc.).

- The FDA has consistently held that granting designations for **artificially narrow subsets would be inconsistent with the intent of the ODA**.

Source: Office of the Federal Register

The ODA's Market Exclusivity Incentive Applies Only to the Orphan Indication

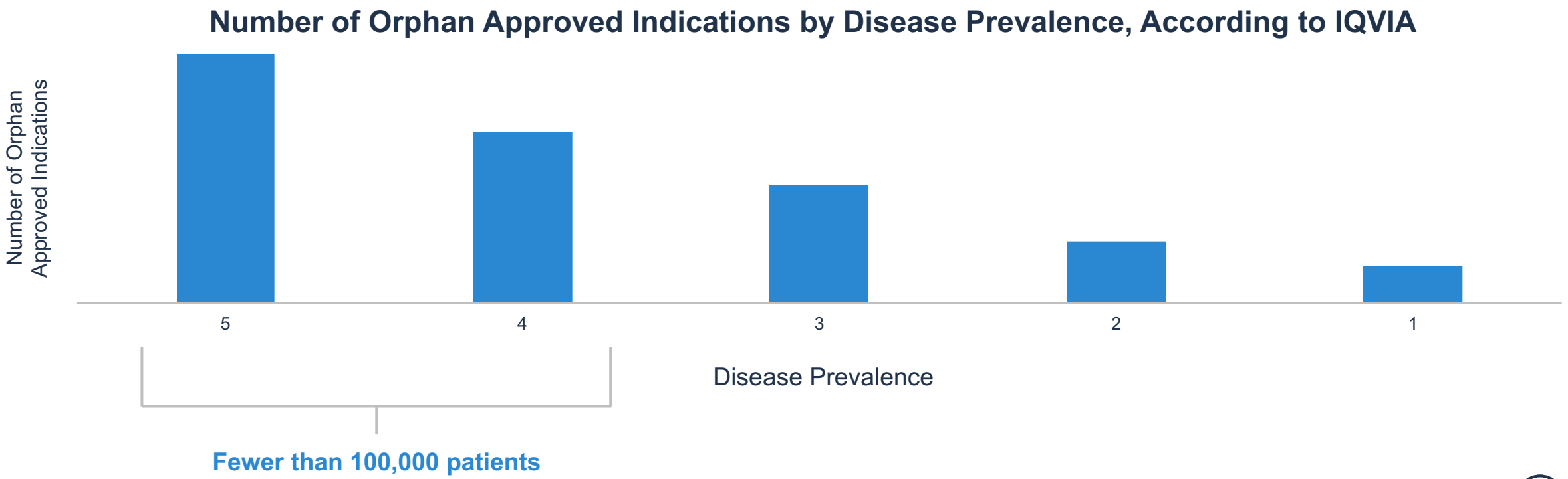
- Orphan exclusivity **only** applies to the orphan-designated indication.
  - It precludes approval of the "same drug" for the designated orphan indication only.
- If an orphan drug goes off-patent (and no other exclusivities apply), generic competition **is permitted** for other indications before the 7 years is up.
- Patents and orphan exclusivity run **concurrently** and are **complementary**.



Orphan Drug Market Dynamics

The Majority of Orphan Drugs Treat Diseases with Patient Populations Under 100,000

According to GAO, 71% of orphan drugs are designated based on populations of less than 100,000, and 50% are for diseases that affect fewer than 50,000. Final approved indications are typically even narrower.

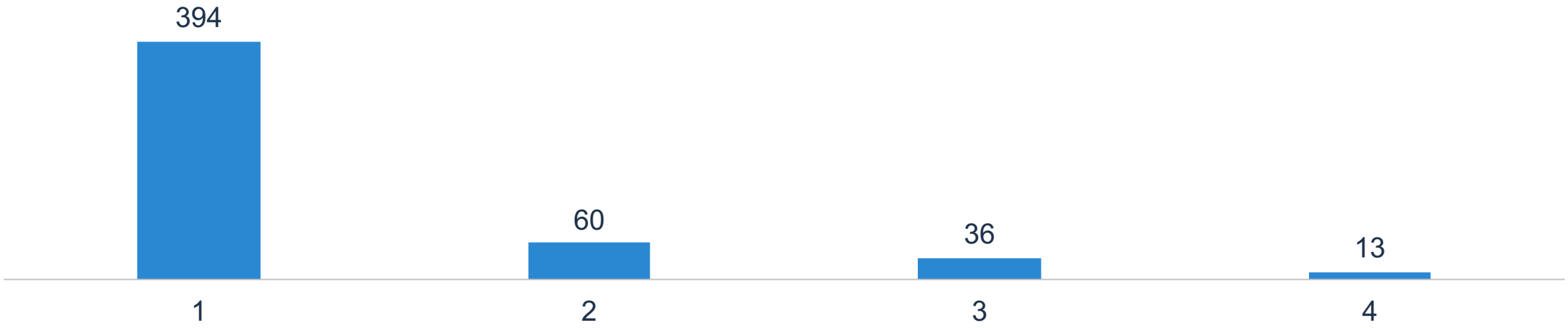


Sources: GAO, IQVIA

Majority of Orphan Drugs Only Treat Rare Diseases

Of the over 500 orphan drugs approved since the passage of the ODA, 78% have been approved only for orphan indications.

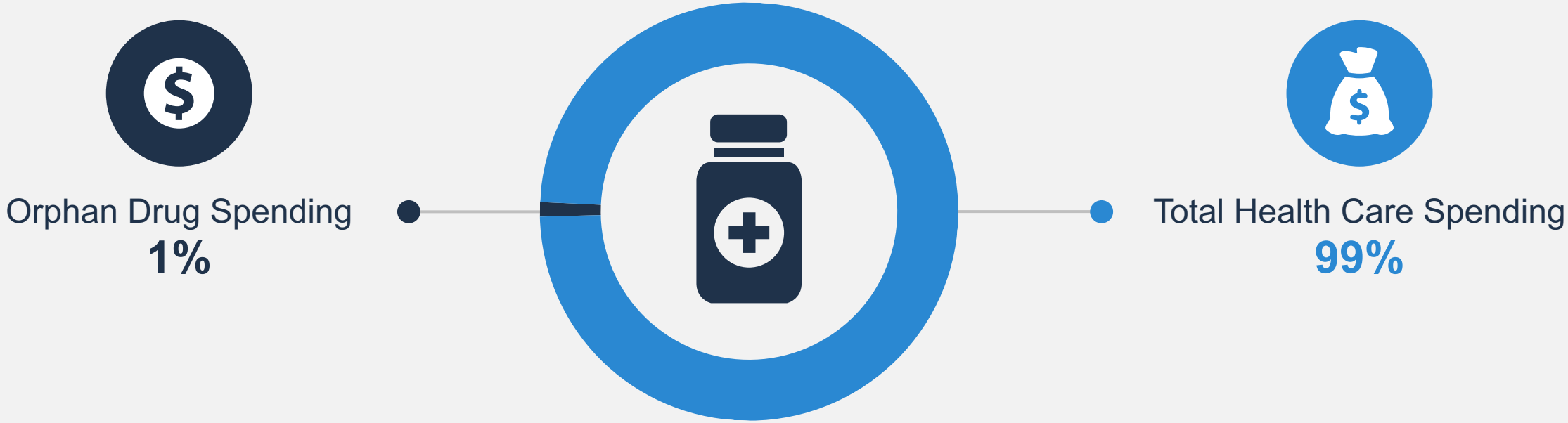
Number of Orphan Drugs Stratified by Approval Sequence, 1983-2018



Source: IQVIA

Orphan Drugs Represented a Small Portion of Overall Health Spending in 2018

Recent studies show orphan drugs for rare diseases represent 9.6% of total pharmaceutical expenditures, or about 1% of total health spending.



Sources: IQVIA, CMS

Payers Are Using Utilization Management Tools to Constrain Spending on Orphan Drugs

A recent study found that payers are increasingly applying utilization management tools to orphan drugs to constrain spending.

Utilization Management Tool	Percentage of Orphan drugs
Tier 4 Placement	**43%**
High Use of Prior Authorization	**34%**

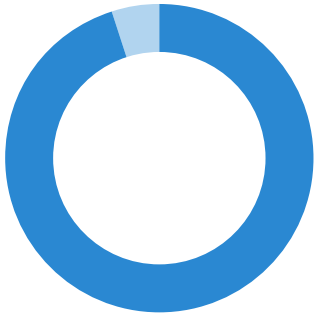
> Payers are stepping up efforts to manage the cost and utilization of orphan drug treatments.
>
> **MANAGED HEALTHCARE EXECUTIVE MAGAZINE**

Sources: Cryts, Cohen & Awatin

Fostering Continued Innovation in Rare Diseases

Continued Investment in Research and Development for Orphan Drugs is Critical

Sustained R&D investment in rare disease drug development is now driving rapid growth in later stage clinical activity. But millions of patients with rare diseases are still waiting for new medicines.



95%

of patients living with rare diseases have no FDA approved treatment options.

Source: Global Genes 2018

Advances in **GENE THERAPY, IMMUNOTHERAPY**, and other areas offer hope for patients with few or no FDA approved treatment options.

Source: Global Genes

Innovative Drug Development Approaches Hold Promise to Speed Patient Access to Medicines for Rare Diseases

Innovative Clinical Trial Designs

Given the unique scientific and practical challenges associated with rare disease drug development, innovative approaches to clinical trials **can enhance efficiencies, allowing for smarter and more targeted, personalized drug development.**

Novel Drug Development Tools

Because 80% of rare diseases are genetic in origin, drug development tools such as biomarkers and novel clinical trial endpoints **hold great promise for accelerating new medicines for rare diseases**.

Patient-Focused Drug Development

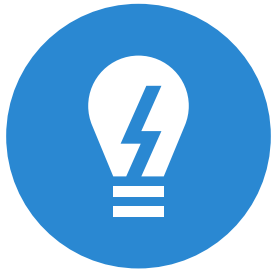
Patients with rare diseases may have unique perspectives on the benefits and risks of potential new medicines and can provide valuable insights on their disease, available treatment options and meaningful measures and outcomes, **providing context for FDA's regulatory decisions.**

Real-World Evidence (RWE)

RWE represents a valuable source of information about the benefits and risks of a medicine in a broader population than could feasibly be studied in a clinical trial, especially for diseases with few patients. Utilizing RWE from multiple data sources **may accelerate the development of new medicines and indications.**

Public Policies Play an Important Role in Fostering Future Orphan Drug Innovation

In addition to the important incentives provided by the ODA, three policy areas are critical for supporting continued investment in biopharmaceutical discovery and development efforts including orphan drugs:



Strong **INTELLECTUAL PROPERTY** protections

A **WELL-FUNCTIONING**, science-based regulatory system

Coverage and payment policies that **SUPPORT AND ENCOURAGE** medical innovation