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

Examples of rare diseases include:

- Amyotrophic Lateral Sclerosis (ALS)
- Sickle Cell Anemia
- Cystic Fibrosis
- Many Types of Cancer

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

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.

<table>
<thead>
<tr>
<th>Obtaining a Diagnosis</th>
<th>Complexity of Care</th>
<th>Emotional and Psychological Stress</th>
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<tbody>
<tr>
<td>• The inherent nature and complexities of rare diseases may mean that an accurate</td>
<td>• Rare diseases often damage many organs and body systems</td>
<td>• Rare diseases take a measurable toll on the emotional and psychological well-being of both patients, their families, and caregivers</td>
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<tr>
<td>diagnosis can take more than seven years after the onset of symptoms</td>
<td>• Multisystem impacts require numerous specialists to manage different aspects of their condition</td>
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<tr>
<td>• Rare disease patients often have to manage complicated care schedules and medication</td>
<td>• Rare diseases take a measurable toll on the emotional and psychological well-being of both patients, their families, and caregivers</td>
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<tr>
<td>regimens</td>
<td>• Logistical challenges related to accessing the often geographically dispersed specialists impacting patient quality of life and productivity</td>
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<td></td>
<td>• Logistical challenges and complexity of care can result in significant impact on caregivers and families</td>
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<td></td>
<td></td>
<td>• Patients can experience feelings of isolation, depression, stress and other issues related to managing their condition impacting quality of life</td>
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The Need for Medical Advances Reflected by Costs for Rare Associated with Diseases with No or Limited Treatment Options

<table>
<thead>
<tr>
<th>Amyotrophic Lateral Sclerosis (ALS)</th>
<th>Sickle Cell Disease (SCD)</th>
<th>Scleroderma</th>
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<tbody>
<tr>
<td>Nervous system disease that weakens muscles and impacts physical function</td>
<td>A group of disorders that cause red blood cells to become misshapen and break down</td>
<td>An autoimmune disease of the connective tissue</td>
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<tr>
<td>• 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</td>
<td>• 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</td>
<td>• Adjusted annual direct and indirect costs of scleroderma in the United States have been estimated at $2.3 billion</td>
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<tr>
<td>• This does not include non-medical expenses and lost income</td>
<td></td>
<td>• It has been estimated that patients lose $300,000 in lifetime earnings because of their condition</td>
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Sources: Resnick, Chodorow and Associates; Obermann & Lyon, American Society of Hematology
Progress Against 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

### 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
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
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.

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

Sources: Channick, R., et al., American Lung Association
A medicine for infant botulism reduces hospitalization length and cost.

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.

54% reduction
In mean length of hospital stay

$88,600 reduction
In hospital charges per patient

Sources: New England Journal of Medicine
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.

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

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**VENTURE CAPITALIST & PARKINSON’S DISEASE PATIENT**
**JONATHAN SILVERSTEIN**

*OrbiMed*

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.

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
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**

<table>
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<tr>
<th>Medicine Type</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Orphan Medicines</td>
<td>11.8 years</td>
</tr>
<tr>
<td>Non-Orphan Medicines</td>
<td>8 years</td>
</tr>
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</table>

*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
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

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 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.

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

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

**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.

**SEVEN-YEAR MARKET EXCLUSIVITY:**
Provides protection from generic competition 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

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.

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

Sources: FDA, Murphy SM et al., NORD, IOM
More than 770 orphan drugs have been approved since passage of the Orphan Drug Act in 1983. However, great unmet need remains.
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
- It has inspired similar legislation in Japan, Australia and Europe

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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*

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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.

**Orphan Drug Designation**
- Company requests designation from FDA at any time during clinical development.

**FDA Review**
- Orphan Drug APPROVAL: Orphan-designated drugs go through FDA review like any other new medicine.

**Available to Patients**

**Drug discovery** ➔ **Preclinical** ➔ **Clinical** ➔ **FDA Review** ➔ **Available to Patients**

- Orphan designation PENDING – company may resubmit with changes
- Orphan designation DENIED – company may submit another application with new information
- Orphan designation GRANTED

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 does **not** prevent generic competition for the same drug in a different indication.
  - It does **not** preclude competing brand drugs in the same therapeutic class.

- 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.
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

- **Orphan Only**: 394
- **Non-Orphan Indication First**: 60
- **Orphan Indication First**: 36
- **Orphan/Non-Orphan Simultaneous**: 13

Source: IQVIA
Recent studies show orphan drugs for rare diseases represent 9.6% of total pharmaceutical expenditures, or about 1% of total health spending.
A recent study found that payers are increasingly applying utilization management tools to orphan drugs to constrain spending.

## Utilization Management Tool

<table>
<thead>
<tr>
<th>Utilization Management Tool</th>
<th>Percentage of Orphan drugs</th>
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<tbody>
<tr>
<td>Tier 4 Placement</td>
<td>43%</td>
</tr>
<tr>
<td>High Use of Prior Authorization</td>
<td>34%</td>
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</table>

Payers are stepping up efforts to manage the cost and utilization of orphan drug treatments.

**Quotes:**

"Payers are stepping up efforts to manage the cost and utilization of orphan drug treatments."
Fostering Continued Innovation in Rare Diseases
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.

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

Source: Global Genes 2018
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.
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**