

From Hope to Healing:

Advancing Rare and Orphan Drug Therapies

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Executive Summary – This article examines the transformative landscape of rare and orphan drug therapies, emphasizing their pivotal role in improving outcomes for over 300 million people worldwide affected by rare diseases. It highlights the exponential growth of this sector, driven by scientific innovation, regulatory incentives, and collaborative efforts. Key advancements such as gene and RNA-based therapies, precision medicine, and AI-driven drug repurposing are explored, alongside challenges related to affordability, equitable access, and sustainability. The article also underscores the importance of strategic acquisitions and licensing agreements in accelerating the development and availability of novel therapies, reflecting the sector's dynamic growth and commitment to addressing unmet medical needs. By analyzing recent industry trends and emerging innovations, it advocates for sustainable policies, global collaboration, and innovative financing models to ensure that progress reaches all patients in need.

Introduction – Rare diseases, often described as medical orphans, present a significant global health challenge due to their rarity and complexity. Affecting fewer than 200,000 individuals per condition in the United States, these diseases collectively impact a staggering number of people worldwide. Despite their rarity, the societal and economic burden of these conditions is profound, making the development of effective therapies an urgent priority. This article delves into the evolution of rare and orphan drug therapies, illustrating how breakthroughs in science, coupled with forward-thinking policies, have transformed a field once considered uneconomical. It examines the intersection of innovation and regulation, the challenges and opportunities in drug development, and the ethical considerations of access and affordability. By spotlighting key achievements and ongoing industry dynamics, the article provides a roadmap for advancing treatments for some of the world's most vulnerable populations.

Understanding Rare Diseases and Their Challenges – Rare diseases are diverse, with over 7,000 identified conditions ranging from genetic disorders like cystic fibrosis to rare cancers such as epithelioid sarcoma and metabolic syndromes like Gaucher disease. These diseases often share common challenges:

- **Limited Knowledge:** Many rare diseases are poorly understood, with fragmented data and delayed diagnoses.
- **Small Patient Populations:** Clinical trials face difficulties in recruitment, leading to longer and costlier development timelines.
- **High Costs:** The niche nature of these therapies often results in significant financial burdens for patients and healthcare systems.

Despite these obstacles, the field of rare and orphan drugs has grown substantially, thanks to innovation and supportive policies.

Statistical Overview – The global orphan drug market has seen exponential growth, valued at approximately \$140 billion in 2020 and projected to surpass \$300 billion by 2030. Regional markets in Asia and Europe are increasingly driving innovation, with robust investment in R&D and policy support. In the United States alone, the FDA granted 370 orphan designations in 2023, reflecting increasing interest and investment in this area.

Regulatory Incentives: A Catalyst for Progress – The introduction of regulatory frameworks, such as the U.S. Orphan Drug Act (1983), European Orphan Medicinal Product Regulation (2000), and similar policies in Japan and other regions, has been instrumental in driving innovation. These initiatives offer:

- **Market Exclusivity:** Up to seven years in the U.S. and ten years in Europe, encouraging innovation by providing developers with a guaranteed period of market dominance. However, this exclusivity often leads to high drug prices, as companies seek to recover development costs within a limited timeframe. Balancing the need for incentivizing innovation with affordability remains a critical challenge.
- **Tax Credits:** For clinical trial expenses.
- **Fee Reductions:** Lower regulatory and marketing approval costs.
- **Grants:** For preclinical and clinical research.

Additionally, programs like the **Rare Pediatric Disease Designation (RPDD)** and the issuance of **Priority Review Vouchers (PRVs)** have added incentives for drug developers, with notable successes such as Onasemnogene abeparvovec (Zolgensma) for spinal muscular atrophy, developed by Novartis and Alglucosidase alfa (Lumizyme) for Pompe disease, developed by Sanofi. These examples underscore the tangible impact of these programs in expediting life-changing therapies to market:

- **RPDD:** Encourages development of treatments for rare diseases primarily affecting children. Drugs granted RPDD can qualify for PRVs.
- **PRVs:** Provide developers with a voucher to expedite the FDA review process for another drug application. These vouchers are often sold or traded within the industry, sometimes fetching hundreds of millions of dollars.

Such measures have contributed to the increasing focus on ultra-rare diseases and pediatric conditions, driving further innovation in this space.

The future of the RPD PRV program remains uncertain beyond its temporary extension to December 20, 2024, pending congressional action on legislation such as the “Creating Hope Reauthorization Act” (H.R. 7384) and the “Give Kids a Chance Act” (H.R. 3433). As of today, according to the FDA, the program will begin to phase out after this date unless a drug has been designated for a rare pediatric disease by December 20, 2024, and approved by September 30, 2026. Advocacy groups are urging Congress to pass a long-term reauthorization to sustain this critical incentive for developing treatments targeting rare pediatric conditions.

Scientific Innovation and Repurposing: Transforming Rare Disease Treatment – Breakthroughs in biotechnology and drug repurposing are redefining the possibilities for rare disease therapies:

- **Gene Therapy:** Products like Onasemnogene abeparvovec (Zolgensma), developed by Novartis, for spinal muscular atrophy (SMA) and Voretigene neparvovec (Luxturna), developed by Spark Therapeutics, for retinal dystrophy caused by RPE65 gene mutations represent a paradigm shift by addressing diseases at their genetic root.
- **RNA-Based Therapies:** Nusinersen (Spinraza), developed by Biogen, for spinal muscular atrophy (SMA) and Patisiran (Onpattro), developed by Alnylam Pharmaceuticals, for hereditary transthyretin-mediated (hATTR) amyloidosis leverage RNA technologies to modulate disease pathways.
- **Precision Medicine:** Targeted therapies, driven by biomarkers and genetic profiling, are enabling tailored treatment approaches.

- **Drug Repurposing and Repositioning:** Drug repurposing has emerged as a cost-effective strategy to accelerate treatment availability for rare diseases. For example, sildenafil (Viagra), initially developed for hypertension, was repositioned to treat pulmonary arterial hypertension (PAH), a rare condition. Similarly, thalidomide, once infamous for its teratogenic effects, is now successfully used to treat multiple myeloma and leprosy.
- **AI-Driven Repurposing:** Artificial intelligence (AI) is further enhancing the potential of repurposed drugs by rapidly analyzing vast datasets to identify new therapeutic applications. Platforms such as BenevolentAI have identified baricitinib, initially developed for rheumatoid arthritis, as a potential treatment for COVID-19 and possibly other rare inflammatory conditions.

Emerging platforms like CRISPR gene editing are also showing immense promise. Intellia Therapeutics is advancing trials for transthyretin amyloidosis (ATTR), a rare protein misfolding disorder, marking a potential revolution in one-time curative treatments.

Challenges and Innovations Driving the Sector – The rare and orphan drug sector is characterized by both substantial challenges and transformative innovations:

1. Challenges

- **Regulatory Complexity:** Navigating varying regulatory requirements across regions can slow drug development.
- **Access and Equity:** High costs and limited manufacturing capacity often restrict global access to orphan drugs.
- **Sustainability:** Ensuring a balance between innovation incentives and affordability remains a critical concern.
- **Diagnosis Gaps:** Many rare diseases are underdiagnosed or misdiagnosed, delaying treatment and care.
- **Limited Natural History Data:** The rarity of these conditions means less robust data to inform clinical trials and treatment decisions.

2. Innovations

- **Adaptive Trial Designs:** Leveraging real-world data and decentralized trials to improve efficiency and inclusivity.
- **Advanced Manufacturing:** Techniques like cell-free synthesis and 3D bioprinting are streamlining production.
- **Omics Technologies:** Genomics, proteomics, and metabolomics are unlocking deeper insights into rare disease mechanisms.
- **Global Collaboration:** Developing countries are adopting innovative frameworks to expand access. For instance, India's Rare Disease Policy aims to subsidize treatments and foster local research.
- **Digital Health Tools:** AI-driven diagnostics and wearable health monitors are improving early detection and treatment personalization. For example, the AI-based platform "Raremark" helps identify patterns in patient symptoms to speed up diagnosis, while devices like Fitbit's Sense monitor vital health parameters that may aid in managing conditions like mitochondrial diseases.

Major Acquisitions and Licensing Agreements (2024) – These strategic moves highlight the sector's dynamic growth and the ongoing commitment to addressing unmet medical needs in rare diseases.

1. Major Acquisitions in Rare and Orphan Diseases

- **Sanofi and Inhibrx (January 2024):** Up to \$2.2 billion deal to obtain INBRX-101, an experimental treatment for Alpha-1 Antitrypsin Deficiency (AATD), with a focus on bolstering the inflammation drug pipeline.
- **Ipsen and Epizyme (March 2024):** A \$450 million deal focusing on rare cancer treatments, including Tazverik for epithelioid sarcoma and follicular lymphoma.
- **AstraZeneca and Amolyt Pharma (March 2024):** A \$1.05 billion deal to boost rare-disease portfolio, including lead candidate eneboparatide for hypoparathyroidism.
- **Gilead Sciences and CymaBay Therapeutics (March 2024):** \$4.3 billion deal for liver disease treatments, including CymaBay's lead candidate, seladelpar, an oral drug for treating primary biliary cholangitis (PBC), a rare, chronic liver disease.
- **Novartis and Chinook Therapeutics (June 2024):** A \$3.5 billion deal focused on developing targeted treatments for rare kidney diseases.
- **Recordati and Sanofi (October 2024):** Acquisition of global rights to Enjaymo, a treatment for cold agglutinin disease (CAD), for \$825 million upfront and up to \$250 million in additional commercial milestone payments.

2. Major Licensing Agreements in Rare and Orphan Diseases

- **Arrowhead Pharmaceuticals and Sarepta Therapeutics (November 2024):** Partnership to develop RNAi therapies for rare genetic diseases affecting muscles, the central nervous system, and lungs, with an upfront payment of \$500 million, a \$325 million equity investment, and potential milestone and royalty payments of up to \$10 billion.
- **Eli Lilly and QurAlis (June 2024):** Lilly secured rights to ASO QRL-204 and other compounds targeting the UNC13A gene for Amyotrophic Lateral Sclerosis (ALS) and frontotemporal dementia in a \$45 million upfront deal, with milestones reaching \$577 million.
- **Novo Nordisk and Neomorph (February 2024):** \$1.46 billion deal for MGDs targeting cardiometabolic and rare diseases.
- **Novartis and PTC Therapeutics (December 2024):** Licensing agreement for PTC518, an experimental Huntington's disease drug, with an upfront payment of \$1 billion and potential milestone payments up to \$2.9 billion.
- **NGM Bio and KdT Ventures (December 2024):** Formation of a NewCo and worldwide license agreement for NGM313, a Phase 2-ready FGFR1c/ β -Klotho agonist drug candidate targeting rare diseases, with potential deal value up to \$608 million.

Economic and Ethical Considerations – Orphan drugs often command high prices, sparking debates about access and affordability. Potential solutions include implementing innovative pricing strategies, such as outcome-based payment models where costs are tied to the effectiveness of the drug, and subscription-based approaches that provide unlimited access for a fixed fee. Policy measures like expanded government subsidies, international collaboration to negotiate prices, and stricter price transparency regulations could also help balance affordability with the need for continued innovation. Therapies like Zolgensma, priced at over \$2 million per patient, highlight the tension between recouping development costs and ensuring equitable access. Key strategies to address these challenges include:

- **Innovative Financing Models:** Subscription-based payment systems or outcome-based pricing.
- **Public-Private Partnerships:** Collaborations between governments, non-profits, and industry to fund development and ensure distribution.
- **Advocacy and Awareness:** Patient organizations play a crucial role in shaping policy and facilitating access to treatments.

Emerging Trends and the Road Ahead – As the rare disease field matures, several trends are shaping its future:

- **Digital Health Integration:** AI and machine learning are accelerating diagnostics and drug discovery.
- **Global Collaboration:** Cross-border regulatory harmonization and data sharing are streamlining development.
- **Focus on Cures:** Advances in cell and gene editing, such as CRISPR, are paving the way for one-time curative therapies.

Conclusion – The orphan drug landscape stands as a powerful testament to the remarkable progress driven by innovation, regulatory foresight, and advocacy. These advancements have already transformed the lives of countless patients with rare diseases, providing not just treatments but a renewed sense of hope. Nevertheless, significant challenges persist in ensuring equitable access, addressing affordability, and fostering global collaboration to bring these breakthroughs to underserved populations. As the sector continues to evolve, there is an urgent need for sustainable policies, innovative financing models, and robust public-private partnerships. The integration of cutting-edge technologies, such as AI, gene editing, and advanced manufacturing, promises to further revolutionize the development of rare disease therapies. Recent strategic acquisitions and licensing agreements demonstrate the strong commitment of key industry players to addressing unmet needs. However, translating these advancements into tangible benefits for all patients will require balanced policies, greater international collaboration, and innovative approaches to ensure accessibility and affordability. By fostering a collective commitment to these goals, we can envision a future where no rare disease and no patient are left behind.

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