Orphan Drug Development

This infographic was designed as a resource for patients and their families to explain the process timelines, and cost to develop a potential therapy for a rare or orphan disease, or an "orphan drug". This is not an exhaustive guide, but a general overview of the steps in the development process. There are resources provided at the bottom of Page 2 for patients and family members who would like to know more.

2 yrs - decades+

Basic Research

First, researchers must learn about the disease they hope to treat; this process is called the **Basic Research Phase** and can take many years or even decades. Most rare diseases are caused by a disrupted biological pathway, and in some rare diseases, more than one pathway is disrupted. Researchers do laboratory experiments to learn about the disease and determine which pathway(s) is affected and how it is different from the "normal" pathway. This work helps scientists determine the best way to treat the disease and what part(s) of the pathway(s) to target. A target is usually a specific gene or molecule, and its role in the disease is confirmed (or validated) through experiments performed on parts of cells (such as DNA, RNA and protein), cells, tissues, or in small animals, such as mice.

Drug Discovery

Once the target is validated, a therapy can be developed during the **Drug Discovery Phase**. Scientists must decide what kind of molecule they want to use and how they will deliver it to the target. To identify the molecule, researchers test many molecules in lab experiments to identify the one with the best properties (e.g. can be manufactured in large amounts, is effective, is not toxic). A potential therapy must then undergo a **proof of concept (PoC) study** using the potential therapy in an animal model to ensure it works as intended.

2 - 5 yrs

Preclinical

Following the PoC, if the therapy proves effective at restoring the disrupted pathway, researchers will move forward with additional testing and manufacturing* as part of the **Preclinical Phase**. Animal studies must be run before testing can be done in humans. A toxicology study will show that the treatment does not cause serious adverse effects in animals. A dose-ranging study must also be run, giving different doses of the therapy to animals in order to find a range of doses that may be effective for human patients. If the therapy shows good results in these studies, it can be submitted to the FDA and/or to regulatory authorities in other countries. The primary goal of this review is to determine if the product is reasonably safe and exhibits biological activity to justify starting human testing.

*Manufacturing typically occurs in parallel with preclinical studies; however this process differs across therapies so specific information for manufacturing is not included here.

Clinical

If the regulatory application has been reviewed without objections, the new therapy will move into human trials. During the **Clinical Phase**, there are significant differences between "standard" and orphan drug development. A first-in-human (FIH) study is run when entering the clinical phase. For rare diseases, FIH trials are usually Phase 1/Phase 2 because there are few patients to support separate trials and gather the maximum amount of information. In a FIH study for a rare disease, researchers may test for safety, tolerability, different dosages, biomarkers and efficacy. Following Phase 1/2, a confirmatory study (Phase 3 trial) may be required*, depending on the therapy, results from the FIH study, and the severity of the rare disease.

2 - 10 yrs

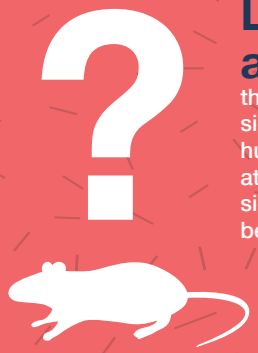
*For very rare, life-threatening diseases for which no therapy exists, and if the new therapy is safe and has a very large treatment effect, a single Phase 1/2 clinical study may be sufficient to obtain market approval.

2 - 3 yrs

Regulation Review, Approval, Launch and Commercialization

If the results from clinical studies show that the therapy is safe, well-tolerated, and effective, applications are filed with various regulatory agencies for approval to market the therapy. The **Regulatory Review** process can be lengthy, although many regulatory agencies provide incentives that expedite the review and approval process for orphan drugs. Once approved, the therapy will have a label (also called prescribing information) that details pertinent information about the medicine. The company that developed the therapy will **Launch** and **Commercialize** it, meaning that the company will connect the patient community to the new therapy and will work with governments and insurance companies to determine if and how the therapy will be covered/reimbursed.

Challenges to Orphan Drug Development



Lack of an animal model

that shows similar signs/symptoms to a human with the disease (or, at minimum, shows signs/symptoms that can be measured and tested)

Control Group not possible or ethical

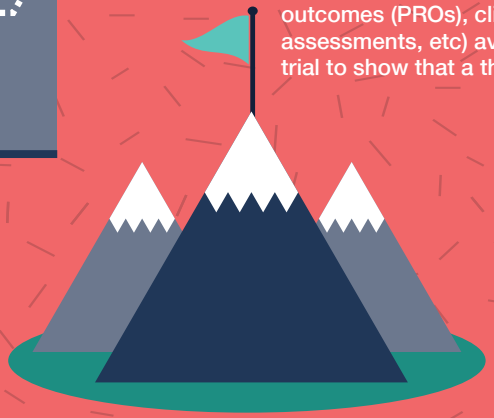
For very rare, rapidly progressive, fatal diseases, there may not be sufficient patients for controlled trials, and there can be ethical concerns with having placebo controls in clinical trials. In these cases, data on the natural course of the disease that are collected outside the trial may be used for comparison.

Poor understanding of the natural history

of many rare diseases (e.g. clinical features, progression, signs and symptoms) means it is difficult to develop new therapies, design clinical studies and determine an appropriate trial duration

Lack of appropriate endpoints

(e.g. lab values, patient-reported outcomes (PROs), clinical exams/ assessments, etc) available for a clinical trial to show that a therapy is effective



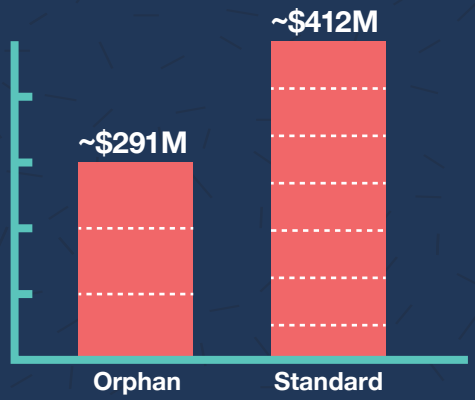
Very small numbers

of people with each orphan disease leading to challenges recruiting enough patients to participate in trials

Challenges securing Government & Insurance Company Reimbursement

for very expensive therapies

Cost of Development



Cost per patient of orphan drugs is high because there are fewer patients being prescribed orphan drugs when compared to "standard" therapies, meaning that fewer patients are available to cover the cost of development.

(Jayasundara et al, 2019)

Additional Resources

Cost of Orphan Drugs vs Standard Drugs
https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0990-4

Global Genes Resources
https://globalgenes.org/resource-hub/

Why do Discovery and Development Take so Long?
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5725284/

Standard Drug Development
https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

the orphan disease center

Penn Medicine