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DRUG DEVELOPMENT AND CLINICAL TRIALS PROCESS:
HOW NEW THERAPIES ARE CREATED AND BROUGHT TO PATIENTS, A SPECIAL FOCUS ON RARE DISEASES

Addressing the Myth that Rare Disease Therapies are Easier to Develop than Therapies for More Prevalent Diseases

Myth: Because rare disease patient populations are so small, clinical trials are much easier to complete.

Fact: Drug development for any therapeutic area is difficult and expensive.[1] In fact, for all therapies, a molecule that enters phase I for clinical testing only has a 9.6% chance of later being approved. That means that fewer than 1 in 10 therapies that begin clinical testing are eventually delivered to patients. For rare diseases, where advances in science have led to developments that can help in identifying the cause of rare diseases, success rates are slightly higher. For rare disease therapies that enter phase I, approximately 25% are later approved.[2] While the rate of success for rare disease is higher, the overall development durations for rare disease applications are four years longer than for all other disease segments.[3]

This graphic outlines the path that all therapies must follow for approval by the Food and Drug Administration (FDA), the regulatory agency in the United States in charge of overseeing the safety and efficacy of therapies, before they are made accessible to patients. The graphic also highlights specific and unique challenges for drug development for rare diseases.

[1] Tufts paper: http://www.marketwired.com/press-release/tufts-center-study-drug-development-assessment-cost-develop-win-marketing-approval-new-2104802.htm

[2] BIO Report: Clinical Development Success Rates 2006–2015.

[3] Tufts CSDD Impact Report: Growth in Rare Disease R&D is Challenging Development Strategy and Execution. 4th ed., vol. 21, 2019, Tufts University

Discovery	Preclinical Testing	Clinical Testing	Approval	Post-marketing
3–5 Years		6–9 Years	1–2 Years	
The discovery phase of drug development involves two stages: **Target Discovery** Identifies processes or sites within the body (such as genes or proteins) that are linked to a disease. **Drug Discovery** Identifies potential therapies that may interact with the identified target. When a promising therapy is identified, it moves to the next stage of the drug development: preclinical testing.	**Preclinical testing is conducted in the laboratory and in animals to learn about the potential therapy in order to determine:** **Safety** Determines whether the potential therapy is safe to test in humans (i.e., toxicology). **Mechanism of Action** Determines how the potential therapy might work in the body. **Potential Dosages** Identifies information on potential dosing to begin testing in humans. Before clinical testing in humans can begin, data from preclinical trials must be reviewed and approved by the FDA. If the results of preclinical testing show that the potential therapy might be safe and effective, an application is filed for approval to begin clinical testing and the potential therapy moves to the next phase: clinical testing.	**Clinical trials evaluate the safety and efficacy of compounds in humans in three phases of testing:** **Phase I Trials** Test safety and determine safe dosages. **Phase II Trials** Include more participants than Phase I trials, focused on both safety, they also evaluate efficacy. **Phase III Trials** Include more participants than phase III trials, study sites, and may be placebo controlled and usually having a much longer duration. Phase III trials focus on confirming safety and longer-term efficacy of the potential therapy. If the results of all three phases meet strict, scientific, clinical, and statistical standards, an application for approval of the potential therapy is submitted to the FDA for regulatory review.	After regulatory and reimbursement coverage approval, the new therapy can be made available for prescribing by a doctor.	Regulatory agencies continue to monitor therapies after approval to collect additional long-term safety information and monitor for unexpected side effects that were not observed during earlier clinical trials. In some cases, a type of trial called a post-marketing surveillance study may be conducted to gather additional information about the drug. The drug may also undergo additional trials designed to test it for safety and efficacy in other patient populations (such as pediatric patients) or for the treatment of other diseases.

Special considerations for rare disease:

Natural history data and knowledge about the disease	Clinical testing	Review and approval	Approval and beyond
• The natural history (how a disease develops and progresses over time) of most rare diseases is not very well understood when compared to more prevalent diseases. This is because only a small number of people are affected by each rare disease, and because these diseases may manifest very differently in different patients. • The relative lack of information about the natural history of a rare disease makes completing the discovery and preclinical phases of drug development very difficult. • In addition to a lack of information regarding the natural history of a disease, there are often times no well-defined mechanisms for measuring how well a potential therapy works. For example, rare diseases do not often have endpoints, outcome measures, or biomarkers which make completing clinical trials and initially diagnosing patients very difficult.	• Rare diseases, by definition, have small patient populations, meaning fewer patients are available to participate in trials. • In fact, a recent report indicates that Phase I trials for rare disease, on average, engaged six times the number of investigative sites to recruit a quarter of the number of patients, compared with those for non-rare diseases. It is estimated that overall development durations for rare disease applications are four years longer than for all other diseases segments.[3] • Additionally, patients available for clinical trials may live far away from each other andfrom the study locations, which may pose logistical difficulties and prevent a clinical trial from enrolling enough patients to result in meaningful data. • If a study cannot enroll enough patients, the study may not be able to attain the high level of statistical proof for safety and efficacy required for approval by the FDA.	• Potential therapies intended to treat rare diseases, or other serious diseases with few or no other treatment options, may be reviewed by the FDA via special, faster pathways and become available to patients sooner. However, it's important to be aware that these faster pathways still require drugs to meet high standards of safety and efficacy.	• Many people with rare diseases face significant challenges in accessing drugs they need to treat their conditions. Uninsured or underinsured patients are at special risk, but even those who have insurance may find that their coverage for rare diseases has limitations.

For Discovery: https://www.fda.gov/ForPatients/Approvals/Drugs/default.htm | For numbers: BIO industry analysis, January 2016

*This chart outlines the general process that potential therapies follow during regulatory review by the FDA. However there are also variations in this process that may include innovative clinical trial designs or expedited approval, for example.