Windeye Partners

Biotechnology & Pharmaceutical Primer:

Understanding the Drug Development Process

Executive Summary

This primer outlines the stages of drug development in the United States, a highly regulated and resource-intensive process. From target identification to post-marketing surveillance, the development cycle spans 10–15 years and can cost up to $3 billion per drug. Given the high failure rate, with less than 1 in 10 clinical candidates making it to market, strategic collaborations and technological innovations are essential to mitigate risk and enhance efficiency.

The Drug Development Process

The drug development process in the U.S. is a lengthy and cost-consuming process, primarily because it focuses on making sure that all drugs that gain approval for sale are not only safe for use but also effective for the intended (and claimed) purpose. Before the creation of the modern U.S. Food and Drug Administration (FDA) in 1938, just a handful of drugs received approval for sale in the United States. Throughout the 1930's and 1940's only about four compounds per year were approved. This number grew to an average of 10 per year through the 1990's and peaked at 59 in 2018. The increase is commendable, but one should keep in mind that, through 2023, only about 1,700 new drugs in total had been approved for sale. Also, drug approvals have fluctuated with 50 in 2021, 37 in 2022, and 55 in 2023.[1]

How a Drug Is Developed

To begin, almost any drug development process must proceed through several stages to create, refine, manufacture, market, and sell a product that is safe, efficacious, and has passed all regulatory approval requirements in the United States. The exact number of stages depends on categorization and classification of the different activities involved, and different schools of thought put it between 6 and 10 separate stages.

But what is more important is the aim and accomplishments of the functional stages of completion, rather than the exact number or grouping, which we will summarize below. As a reminder, drug development is not a fast or inexpensive venture, consuming a great deal of time and resources, which can explain why many pharmaceuticals may carry such high price tags.

[1] FDA Center for Drug Evaluation and Research

Stage 1 – Identification and Validation

This is the time at which small molecules or biological compounds, often a gene or protein, are identified and selected for development as leads for any given disease. Following the identification of such molecules, researchers will then also confirm that the molecule(s) are indeed related to the disease in question. If a molecule shows promise as a therapeutic, it must then be characterized as to size, strength(s), and weakness(es), as well as undergo thorough screening regarding conditions to maintain function, including acute, repeated dose, genetic and reproductive toxicity, carcinogenicity, and bioactivity studies. The formulation must remain potent, sterile, and safe (nontoxic) to continue. Improvement or refinement of hit compounds that have been identified as "leads" is then focused on in terms of efficacy, exposure safety, potency, and stability. At this stage, it is not uncommon for developers to have several compounds on hand.

Stage 2 – Preclinical Development

At this stage, the testing of the "lead" candidates is conducted which is primarily broken down into two parts: in vitro and in vivo testing; in vitro refers to the interaction of the molecules in a test tube and lab setting while in vivo refers to testing on animals and other living cell cultures. Such evaluations have also come to be labelled as "IND enabling studies" since the end result and goal of the testing in the preclinical stage is completing the data required and preparation of an Investigational New Drug (IND) application.

While efficacy is beginning to be established, safety is a primary concern, as preclinical studies will be prohibited by the FDA from moving into clinical trials without extensive data on safety. In addition to all molecule composition and testing to date, the IND must include a full scale-up manufacturing of the "leads" for human clinical trials for application and submission to the FDA. At this time, researchers will be dealing with anywhere from 1 to 5 candidates and not the hundreds with which they may have begun.

Stage 3 – Investigational New Drug Application (IND)

The third step involves submitting a request to the FDA for authorization to administer such an experimental drug or biological product in conducting clinical trials on humans. The FDA will scrutinize the results of preclinical testing, focusing on safety, side effects, chemical structure, and relationship to promising results, as well as manufacturing processes for the drug. The application and authorization must precede the start of clinical trials, and only if the FDA approves the IND can a company proceed.

Stage 4 – Clinical Trials

Phase 1 Clinical Trial

Often referred to as the "Human Pharmacology" stage, this is the first time that studies are conducted to determine the safety and pharmacokinetics (which is concerned with the

movement of drugs in the body) of the drugs in what is generally a limited number of healthy humans. The primary focus will be on safety regarding how the drug is absorbed and eliminated from the body, possible side effects of increasing, continued, or maximized doses, and whether it is producing the desired results.

Phase 2 Clinical Trial

Also known as the "Therapeutic Exploratory" stage, it encompasses studies conducted to evaluate the effectiveness of a drug for a particular disease or signs or symptoms in patients with the condition under study. In addition, the largest difference between Phase 1 and Phase 2 trials is that the patient population is increased from 15-30 to several dozen or even 100+, and the patient pool is not healthy humans but those afflicted with the ailment of focus. As earlier, safety remains a preeminent concern, but the focus begins to shift towards efficacy. During Phase 2 trials, optimal dosing is also examined. At this point, we should keep in mind that most NMEs fall off the testing radar during Phases 1 and 2, leaving only a small remaining number of compounds viable for Phase 3.

Phase 3 Clinical Trial

In what is known as the "Therapeutic Confirmatory" stage of the Clinical trials, safety continues to be a priority, but the primary intent is to gather additional information to evaluate the overall risk-benefit trade-off posed by the use of the drug in afflicted patients. In other words, to what degree is the compound able to alleviate or, at best, eradicate the symptoms or cause(s) of the disease so that its use has a positive outcome for those suffering? Phase 3 trials are designed by researchers but must be approved by the FDA prior to starting and generally contain formal guidelines and defined endpoints or milestones to determine the success or failure of a proposed drug compound. Phase 3 trials include a much larger patient base, typically in the hundreds or in some cases, even thousands, and are the longest in duration and most costly of all clinical trials. At this point, researchers are not only focused on determining definitive efficacy but also on future manufacturing potential if the results are encouraging. If the experimental drug meets its designated endpoint(s) and can prove to be safe for use by patients, the researchers begin the arduous task of filing for its approval.

<u>Stage 5 – New Drug Application (NDA) Filing</u>

The New Drug Application (or, in the case of a biologic product, a Biologic License Application – BLA) is submitted to the FDA for approval of use and must include all research and safety data observed during the prior steps. The application also includes manufacturing scale-ups and marketing in designated countries. If the NDA is accepted, a *Prescription Drug User Fee Act* (PDUFA) date is established 10 months from that date, at which time the FDA is expected to make a decision.

Stage 6 – PDUFA Date and Decision

The FDA and its related agencies generally wait until the PDUFA date to release their findings and decision. There are three potential outcomes: outright denial, request additional information through issuance of a *Complete Response Letter* (CRL), or approval. Outright denial is rare. Receipt of a CRL states what was lacking in the findings and/or application that prevented the drug from being approved and offers suggestions on how to remedy the situation. This often requires the researchers to conduct additional studies and/or alter the proposed manufacturing process in order to gain FDA approval. The NDA is then resubmitted, and if the FDA approves the drug, it becomes immediately available for commercial production and marketing.

Stage 7 – Phase 4 Clinical Studies/Post-Marketing Trials

Even after a drug is approved and sold in the U.S. market, the drug developer cannot simply focus on the manufacture and marketing of the compound, and it is not uncommon for the FDA to request long-term safety studies. Such studies, often called Phase 4, are designed to provide additional information on the drug, which may include the risks, benefits, use, and optimal dosing. The studies may be voluntarily conducted or as required by the FDA and other regulatory agencies.

Summary

In summary, developing a drug is not a simple, quick, or affordable process. A typical estimate from the point of identifying compounds to drug delivery to the public is 12 years, but this can vary depending on the complexity of the compound. According to a 2020 study published by JAMA Network,[2] the average cost associated with the process is $1.3 billion (median $985 million). Only 5 in 5,000 drugs (0.1%) that enter preclinical testing progress to human testing, and only one of these 5 drugs that are tested in humans is approved. Hence, the odds of a new drug making it to market are approximately 1 in 5,000 (0.02%).

For this and other reasons there has been an increasing emphasis on the idea of private or public companies pairing with and working in conjunction with universities, governments, and other entities in the pharmaceutical (genetic, technology, NGO research and think-tanks) field to collaborate resources and share costs to make it a more affordable and efficient process yielding more effective prescription drugs at a faster pace and with a price that is accessible to a greater number of consumers. The increased use of AI-driven drug discovery processes may also help speed up development and lower costs.

[2] Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018