

Chapter Six:

Drug Development



After the lengthy process of drug discovery (identifying a target and validating a drug candidate), the process of drug development is still far from complete. Drug development includes the safety, efficacy, formulation and manufacture of the drug. Typically, safety testing begins with a series of experiments called **preclinical studies**. If these studies predict the drug candidate to be safe, testing begins in humans in a series of studies called **clinical trials**.

Preclinical Studies

Preclinical studies are tests that take place in a scientifically controlled setting using cell cultures and animals as models. The goal of preclinical studies is to predict what the body does to the drug candidate (**pharmacokinetics**), what the drug candidate does to the body (**pharmacodynamics**), and whether the drug candidate may pose potential health hazards or toxic side effects.

Pharmacokinetic testing provides data to answer questions such as: How is the drug absorbed and transported? Which cells and organs are affected? What enzymes in the body break down the drug, and how fast does this occur? How is the drug or its metabolites (breakdown products) eliminated from the body? Pharmacodynamic studies examine dose-response effects and often monitor biochemical and physiological changes (such as enzyme activities, heart rate, blood pressure and body temperature) in the test subject. Pharmacodynamic testing, which shows what the body does in response to the drug, is used to answer the question: Is the drug harmful or toxic to cells or organ systems? Toxicology studies address the potential of the drug or its metabolites to kill or damage cells and organs, cause cancer or cause reproductive problems, including birth defects or sterility. Pharmacokinetic and pharmacodynamic studies are used together to reach the goal of preclinical studies, which then answer the question: Is the drug safe? In the United States, preclinical studies must be conducted under FDA guidelines known as current Good Laboratory Practice. Many other countries follow global harmonized regulatory guidelines as well.

Information from these studies is vital. It allows researchers to estimate a safe dosage level for humans in phase 1 clinical trials. Although drug companies are required to submit animal model data to regulatory agencies as part of the drug approval process, companies are taking steps to reduce the number of animals used in testing because of ethical concerns and the cost associated with facilities.

In the United States, institutes that conduct research involving animals and that receive federal funding must have an Institutional Animal Care and Use Committee (IACUC). This committee reviews research protocols and evaluates the care laboratory animals receive. The IACUC is responsible for making sure labs comply with the Animal Welfare Act.

Animal models greatly enhance scientists' ability to test the effectiveness and safety of new drug candidates. In target validation, researchers may use **knock-out mice** and/or **knock-in mice** to validate a target. Knock-out mice are genetically altered to remove mouse versions of human disease genes. Human disease genes can also be knocked in to create mouse models with human diseases like cancer, diabetes, Alzheimer's and Parkinson's. Drug candidates are tested on these mice, enabling researchers to check for adverse side effects before giving the candidate drug to humans.

Initially, many studies of drug safety and toxicity are done using **cell lines**. Cell lines are engineered to express genes that are often responsible for adverse reactions. The creation of cell line models has decreased the number of animals needed for testing (reducing cost and time) and helps accelerate the drug development process.*



*For more information on Amgen's commitment to ethical use of animals in research, visit www.amgen.com/science/ethical_research.html.

How Is Dosage Determined?

There are two types of phase 1 dosage studies: SAD studies and MAD studies.

SAD: Single-Ascending-Dose Studies

A few volunteers are given a small dose of the investigational new drug and observed. If there are no adverse reactions, another group is given a slightly higher dose. This is repeated as many times as needed until volunteers start to exhibit intolerable side effects. At these dosage levels, the investigational new drug is said to have reached maximum tolerated dose (MTD).

MAD: Multiple-Ascending-Dose Studies

The same volunteers receive higher and higher doses of the investigational new drug until the dosage reaches a certain level. Samples of body fluids are collected with each increase in dosage level to understand how the body processes the investigational new drug.

Phase 1 clinical trials are usually conducted in an inpatient clinic where full-time staff can observe the study subjects.

If preclinical trials provide sufficient evidence that a drug candidate is safe, companies submit an **Investigational New Drug (IND)** application to the FDA. After the FDA approves the IND, companies can begin phased clinical trials in humans.

Clinical Trials

Clinical trials are tests designed to determine the safety, proper dosage, efficacy, adverse reactions and long-term-use effects of a new drug in human subjects. Clinical trials taking place in humans are conducted under global harmonized guidelines, such as the FDA's **current Good Clinical Practice (cGCP)**, which protects the rights and ensures the safety of human test subjects and follows the U.S. Code of Human Research Ethics.

Clinical trials are conducted in three successive phases—1, 2 and 3—and test progressively larger numbers of humans in each phase. Each phase has a different purpose and helps researchers answer different questions. If a phase is successful, the drug candidate proceeds to the next phase. If unsuccessful, clinical trials are halted, the drug is suspended and the sponsor company returns to the discovery phase to look for another drug candidate.

Clinical trials are conducted at different testing sites. It takes several years to complete all three clinical trial phases.

Clinical trials are often managed by a contract research organization (CRO), which is an independent organization. The CRO is responsible for all the data management and communication between the sponsor company and physicians overseeing the clinical trials. The CRO also ensures that the study volunteers understand and accept the risks

involved in the clinical trials and that cGCP guidelines are followed.

BIOFACT



A crucial component of initiating a clinical trial is recruiting study subjects who agree to participate and sign a document called informed consent. Potential subjects must be informed about all aspects of the study before they decide to participate. Participants can withdraw their informed consent at any time.

Phase 1

Phase 1 trials represent the first time an investigational new drug is tested on humans. The goal is to evaluate the drug's safety, tolerability and safe dosage range. The testing group is often small, ranging from 20 to 50 volunteers. These are usually healthy volunteers who do not have a disease. However, sometimes patient volunteers will be accepted into a phase 1 clinical trial, particularly when testing oncology therapeutics. Usually these patients have been unsuccessful with available treatments or have few treatment options, or the drug's potential side effects are too risky to involve healthy subjects (such as using some chemotherapeutic agents).

Phase 2

The goal of phase 2 trials is to determine the efficacy and safety of the investigational new drug among a larger group of patient volunteers—usually 100 to 300 people.

A patient volunteer is someone who has the disease the drug is intended to treat. Some companies divide phase 2 trials into phase 2A (to assess dosage) and phase 2B (to assess efficacy). Most investigational new drugs fail during this stage because of efficacy and/or safety issues.



Phase 3

The goal of phase 3 trials is to confirm the effectiveness of the investigational new drug and compare it with placebos or therapies already available on the market. To do this, hundreds or thousands of patient volunteers are tested. Phase 3 trials are the most expensive and time-consuming, lasting for a couple of years or longer to establish long-term safety.

Once phase 3 is successfully complete, the sponsor company files a new drug or biologics application with the country's regulatory agency. In the United States, the company would file a New Drug Application (NDA) for a small-molecule drug or a **Biologic License Application (BLA)** for a large-molecule drug with the FDA. If the governing regulatory authority (the FDA in the United States or the European Medicines Agency, known as the EMEA, in Europe) approves the drug, the sponsor company is permitted to market and sell the product in the country or countries regulated by that authority. The final manufacturing of the drug—or large-scale production—

must take place in a facility that meets the country's strict guidelines, such as the FDA's current Good Manufacturing Practice (cGMP), to ensure safety and purity of the product.

BIOFACT



One of the largest challenges associated with clinical trials is the shortage of study subjects.

Phase 4

Phase 4 trials occur after an approved drug is on the market. A goal is to monitor the drug's safety and efficacy when utilized in a normal medical setting in a population of patients that could number in the millions. Sometimes adverse reactions, which were not seen in a comparatively small cohort of patients (3,000 patient volunteers as compared to millions), are discovered in larger and more diverse populations. If an adverse reaction is discovered, the drug may be withdrawn from the market. Either the sponsor company can voluntarily withdraw the drug or a regulatory body can pull the drug from the marketplace. After further testing, the drug may or may not be reinstated.

The stages in product development, or **product pipeline**, take, on average, 10 to 15 years to complete. Most investigational drugs do not make it. Out of every 1,000 potential new drugs in discovery, only one will make it to approval.

Study Designs

Late-stage trials often include a double-blind randomized controlled test. In this type of study, neither the patient volunteer nor the researcher knows which volunteer belongs to the control group or the experimental group. Each patient volunteer is randomly placed into one of the groups. A third party keeps this documentation and releases it only after the study is over.