Research and Development

Drug Discovery

Scientists' knowledge of disease is growing rapidly and today they are tackling diseases more complex than ever before. Armed with some understanding of how the disease works, the first step in making a new medicine is to identify a specific target that is a promising focal point for a medicine - for example, a molecule that plays a crucial role in a particular disease.

Teams of chemists, pharmacologists and biologists then screen thousands of compounds - or chemically or genetically engineer new ones - to generate "lead compounds." These molecules have some desirable properties, but researchers usually must modify them to increase activity or minimize side effects - a process called "lead optimization." Out of this process come hundreds of potential drugs.

In choosing compounds for further testing researchers must weigh basic concerns: Is it likely to be more effective than current therapies? Will it be possible to manufacture? Does it have a reasonable dose range and delivery system (e.g., oral, inhaled)? To find the right molecule scientists must have plenty of ingenuity and diligence, but a little serendipity can help, too.

Even after a medicine is discovered teams of engineers, biologists, chemists and physicists must spend long hours figuring out how to mass produce the results achieved by an individual scientist at his or her lab bench. Often promising experiments are not replicable on a large scale -the reaction may give off extreme heat, or cause an explosion, or release a toxic gas. The research may fail because it is not possible to manufacture the drug safely or to the proper specifications.

Preclinical Testing

Once a drug candidate has been identified in the laboratory, it begins years of testing. It starts with lab and animal studies to evaluate its safety and demonstrate that it has biological activity against the disease target.

Key preclinical tests include *pharmacokinetics,* the study of how drugs move through living organisms. Scientists examine four key processes - absorption, distribution, metabolism and excretion - to ensure that the medicine reaches its intended target and passes through the body properly.

In addition to biological tests, researchers conduct a number of other preclinical studies. Chemistry tests establish the compound's purity, stability and shelf life. Manufacturing tests determine what will be involved in producing the medicine on a large scale. And pharmaceutical development studies explore dosing, packaging and formulation (e.g., pill, inhaler, injection).

The main goal of preclinical studies is to rigorously assess safety before human tests begin and this can take anywhere from 3-6 years. Some preclinical safety tests continue even after the start of clinical trials in people to determine if there are any long-term adverse effects researchers should look for.

Investigational New Drug (IND) Application

After preclinical testing is completed, a company files an IND with the U.S. Food and Drug Administration (FDA) prior to beginning any human testing.

The application must show results of preclinical experiments; the chemical structure of the compound; how it is thought to work in the body; any side effects found in animal studies; and how the compound is manufactured.

The IND must also include a detailed clinical trial plan, including how, where and by whom the studies will be conducted. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted. Progress reports on clinical trials must be submitted at least annually to FDA and the IRB.

[The IND becomes effective, and clinical trials can proceed, if the FDA does not disapprove it within 30 days.]

Clinical Trials

In clinical trials teams of physicians carry out studies designed to determine if the drug is safe in people and an effective treatment for the disease in question. Of the 250 compounds that enter preclinical testing, only five will make it this far.

There are three phases of clinical trials:

- **Phase I:** The medicine is tested in a small group (20-100) of healthy volunteers - often in a hospital setting - to determine its safety profile, including the safe dose range. Pharmacokinetic studies examine how a drug is absorbed, distributed, metabolized and excreted, as well as the duration of its action. Phase I studies can take from six months to one year to complete.
- **Phase II:** Placebo-controlled trials involving approximately 100 to 500 volunteer patients who have the disease being studied. The goal of this phase is to establish the "proof of concept" - i.e., the medicine effectively treats the disease. Researchers continue to evaluate the drug's safety and look for side effects, and determine optimal dose strength and schedule (e.g., once or twice daily). Phase II studies can take from six months from one year to complete.
- **Phase III:** The medicine is tested in large, randomized, placebo-controlled trials with much larger numbers of patient volunteers - from 1,000 to 5,000, in hospitals, clinics and/or physician offices - to generate statistically significant data. Researchers closely monitor patients at regular intervals to confirm that the drug is effective and identify side effects (also called adverse events). Phase III studies can take from one to four years to complete, depending on the disease, length of the study, and the number of volunteers.

While Phase I-III studies are taking place, researchers are also conducting a number of crucial parallel studies: toxicity tests and other long-term safety evaluations; dosage forms; plans for full-scale production; package design; and preparation of the complex application required for FDA approval.

New Drug Application (NDA)

Once all three phases of the clinical trials are complete, a company analyzes all of the data. If the findings demonstrate that the experimental medicine is both safe and effective, the company files an NDA with the U.S. Food and Drug Administration (FDA).

NDAs typically run 100,000 pages or longer, just one illustration of the extensive testing a medicine must go through in order to gain FDA approval. They contain all of the information about all of the studies - including preclinical testing, all clinical trials, dosing information, manufacturing details and proposed labeling for the new medicine.

FDA Review/Approval

In this final stage, the FDA scientists review all the results from all the studies carried out over the years and determine if they show that the medicine is safe and effective enough to be approved.

Depending on the medicine or disease in question, the FDA sometimes convenes an Advisory Committee meeting. These independent panels of experts, appointed by the FDA, consider data presented by company representatives and FDA reviewers. Committees then vote on whether the FDA should approve an application, and under what conditions. The FDA is not required to follow the recommendations of the advisory committees, but they often do.

If the medicine is approved, or "cleared for marketing," it becomes available for physicians and patients.

It took an average of 16.9 months for the FDA to review each medicine it approved in 2003. The proportion of rejected applications has remained constant over the years at about 10% to 15%.

Ongoing Studies

Even after approval, the studies and observation continue. A much bigger group of patients may begin to use a medicine upon approval compared with the thousands of patients in clinical trials and in this larger scale rare side effects may occur, so companies must continue to monitor the drug carefully. The FDA requires them to continue to submit periodic reports, including any cases of adverse events (side effects or complications).

Sometimes, the FDA requires a company to conduct additional studies. Known as Phase IV or "post-marketing" studies, they evaluate long-term safety or generate more data about how the medicine affects a particular group of patients (e.g., children or the elderly).

Phase IV studies can continue for years; one study can cost between $20-30 million. Depending on the findings, a company can use the studies to submit a Supplemental NDA, seeking additional indications for the medicine.