The Process of Bringing a New Drug to the Market

Information prepared by the Alzheimer's Association

Every year, about 1.6 billion prescriptions are filled in the U.S. - an average of seven few every man, woman and child. There are more than 2,500 different prescription drugs now available in the U.S. For each prescription drug on the market, hundreds of thousands of chemical compounds are made and tested. For a new drug to progress from an idea to the pharmacist's shelf, it can take up to 12 years and $231,000,000. Each drug must pass a series of testing phases with guidelines set by the Food and Drug Administration (FDA).

Preclinical Testing
The first step in developing a new drug is preclinical testing, which includes all studies that take place before a drug is tested in humans. The goal of preclinical testing is to screen chemical compounds for potential benefits, and rule out those with severe or dangerous side effects. In this stage, laboratory tests and animal studies are performed to determine the drug's properties and how it works in a living organism. Researchers conduct early laboratory tests to learn how the drug interacts with various substances "in the test tube." For instance, if a drug is designed to protect nerve cells from damage it will be tested on nerve cells grown in the laboratory to learn whether it performs as desired.

Once researchers gather initial data on the drug's properties, they can test the drug in animals. Through animal tests, researchers attempt to discover how the drug acts in a living organism, so they can try to predict how it will work in humans. They perform tests to discover possible harmful side effects at varying doses. Using the results of animal tests, researchers will try to explain how the drug is absorbed into the blood, how it is broken down. And how quickly its breakdown products are eliminated from the body. During these tests, researchers may slightly alter the drug's chemical structure to try to make it work more efficiently. Testing drugs in animals is extremely important not only to ensure that a drug works the way researchers desire, but also to make sure that humans aren't given a drug that could cause damage. The extensive data needed from these preclinical tests usually takes one to two years to acquire.

The Investigational New Drug Application
If preclinical data indicates that the drug has potential to treat a specific disease(s), that pharmaceutical company developing it files an investigational new drug (IND) application with the FDA. The IND explains the results of all experiments, the drug's chemical structure, how it is manufactured, how it works in the body, any known toxic effects, and the results of any previous human use. In addition to all past work, the IND must contain plans for human drug studies--the number of patients to be studied, patient selection criteria, names and locations of researchers performing the studies, and what safety and effectiveness measurements will be used to evaluate the drug.

The next step is to test the drug in human volunteers. Usually, there are three phases of human testing. Each phase involves a greater number of people and builds on findings from the previous phase.
Phase I Testing
Phase I typically involves 20-100 normal, healthy volunteers, and is mainly concerned with learning more about the safety of the drug. As in animal studies, researchers attempt to answer questions about how the body absorbs, breaks down, and eliminates the drug. Various tests are performed to determine the drug's effects on different organs and tissues. Any side effects that occur must be documented. These initial studies are critical to the design of later drug studies; they provide essential information about what dose at the drug can be given safely, how often it can be given, and whether any precautions need to be taken (such as not drinking alcohol or eating certain foods). The number of individuals exposed to the drug is increased gradually as safety is determined; therefore, phase I studies may last from six months to a year or more. One of the most common reasons for a drug to fail phase I testing is evidence that it is toxic at doses too small to produce any beneficial effect.

Phase II Testing
Once phase I studies show that a drug is reasonably safe, phase II studies may start. In phase II, researchers begin to evaluate the drug's effectiveness in small numbers of patients (typically 100-300) with the targeted disease or condition. This phase of testing frequently consists of double-blind, placebo-controlled studies. A placebo-controlled study compares the effects of the experimental drug in one group of patients to that of a placebo ("sugar pill") in an identical group of patients. A double-blind, placebo-controlled study is one in which neither the patients nor the researchers know who is receiving the drug and who is receiving the placebo. When patients enroll in a double-blind, placebo-controlled study, they are randomly assigned to one of two or more groups—drug or placebo. The study is performed, with all changes in patients' conditions being carefully recorded. After the study period is over, researchers break the code and analyze the results to determine whether any patients receiving the drug demonstrated changes different from those receiving the placebo. This double-blind, placebo-controlled design is particularly important in developing drugs for Alzheimer's disease, because it prevents researchers from attributing changes caused by other factors, such as the patient's mood or researcher's expectations, to the effects of the drug. In order to determine effectiveness of a drug, there is no substitute for a double-blind, placebo-controlled study.

Phase II studies also attempt to reveal side effects that occur with short-term administration of the drug. Most drugs affect systems in the body other than the one(s) for which they are intended (e.g., some Alzheimer drugs have liver side effects). Sometimes these side effects are not apparent to the patient, sometimes they are apparent but tolerable, and sometimes their severity outweighs the drug's benefits. Animal testing and phase I testing usually expose any potentially life-threatening side effects, but as a drug is given to larger numbers of patients, new side effects are often discovered. Phase II testing may last from several months to two years. It is not uncommon for a drug to be dropped from testing sometime around this phase, either because of side effects, little or no benefit, or the development of better drugs.

Phase III Testing
By the time a drug reaches phase III, researchers have collected a good deal of information about its safety and effectiveness. Results of previous phases should show whether it has some therapeutic effect. Most of the drug's common short-term side effects and adverse reactions should be recorded. In phase III, researchers are primarily concerned with learning further details about proper use of the drug. For example, phase I and phase II studies usually aren't designed to provide information about the best doses and timetables for administration of the drug. Also, data on long-term safety in patients has yet to be obtained. In phase III, researchers
test the drug in *larger* numbers of patients for longer periods of time to get an idea of how the drug will work in ordinary medical practice. For many diseases, phase III studies involve 1,000 to 3,000 patients, and last two to four years. Studies in this phase almost always use the placebo-controlled, double-blind design. The results of phase III studies clarify benefit-risk relationship, uncover less common side effects, and help to show how physicians should prescribe the drug. If a drug fails phase III, it is usually because studies have failed to show clear evidence that it is effective and/or safe.

**The New Drug Application**
After successfully completing all three phases of testing, the pharmaceutical company can file a New Drug Application (NDA) with the FDA. The NDA contains all the scientific information that researchers have gathered—often 100,000 pages or more detailing the chemical structure of the drug, animal and laboratory studies, all human test results, how the drug is manufactured, and prospective prescribing information. The FDA uses the information contained in the NDA to determine whether the drug is effective and safe enough to be available to the public. Since the FDA often finds that it needs further information or needs to have more than one review, the average time before a decision is made is about two years. The FDA has recently announced that it will attempt to reduce the time needed for this review process.

**Marketing Approval**
Once the NDA is approved, the drug becomes available for prescription. However, the pharmaceutical company's part is not over. They must submit periodic reports to the FDA, including descriptions changes in frequency or severity of side effects. For most drugs, the FDA requires additional studies to evaluate long-term effects.