

OHRS Information Sheet

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The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

The path a drug travels from a lab to your medicine cabinet is usually long, and every drug takes a unique route. Often, a drug is developed to treat a specific disease. An important use of a drug may also be discovered by accident.

For example, Retrovir (zidovudine, also known as AZT) was first studied as an anti-cancer drug in the 1960s with disappointing results. It wasn't until the 1980s that researchers discovered the drug could treat AIDS, and the Food and Drug Administration approved the drug, manufactured by GlaxoSmithKline, for that purpose in 1987.

Most drugs that undergo preclinical (animal) testing never even make it to human testing and review by the FDA. The drugs that do must undergo the agency's rigorous evaluation process, which scrutinizes everything about the drug--from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured.

Stages of Drug Development and Review

Investigational New Drug Application (IND)--The pharmaceutical industry sometimes provides advice to the FDA prior to submission of an IND. Sponsors--companies, research institutions, and other organizations that take responsibility for developing a drug--must show the FDA results of preclinical testing they've done in laboratory animals and what they propose to do for human testing. At this stage, the FDA decides whether it is reasonably safe for the company to move forward with testing the drug in humans.

Drug Review Steps

1. Preclinical (animal) testing. Pre-IND
2. An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3. Phase 1 studies (typically involve 20 to 80 people).
4. Phase 2 studies (typically involve a few dozen to about 300 people).
5. Phase 3 studies (typically involve several hundred to about 3,000 people).
6. The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.
8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
10. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug).
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the application or find it either "approvable" or "not approvable."

Clinical Trials--Drug studies in humans can begin only after an IND is reviewed by the FDA and a local institutional review board (IRB). The board is a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research.

IRBs approve the clinical trial protocols, which describe the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study's objectives, and other details. IRBs make sure the study is acceptable, that participants have given consent and are fully informed of their risks, and that researchers take appropriate steps to protect patients from harm.

Phase 1 studies are usually conducted in healthy volunteers. The goal here is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted. The number of subjects typically ranges from 20 to 80.

Phase 2 studies begin if Phase 1 studies don't reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment--usually a placebo or a different drug. Safety continues to be evaluated, and short-term side effects are studied. Typically, the number of subjects in Phase 2 studies ranges from a few dozen to about 300.

At the end of Phase 2, the FDA and sponsors try to come to an agreement on how the large-scale studies in Phase 3 should be done. How often the FDA meets with a sponsor varies, but this is one of two most

common meeting points prior to submission of a new drug application. The other most common time is pre-NDA--right before a new drug application is submitted.

Phase 3 studies begin if evidence of effectiveness is shown in Phase 2. These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people.

Postmarketing study commitments, also called Phase 4 commitments, are studies required of or agreed to by a sponsor that are conducted after the FDA has approved a product for marketing. The FDA uses postmarketing study commitments to gather additional information about a product's safety, efficacy, or optimal use.

New Drug Application (NDA)--This is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

When an NDA comes in, the FDA has 60 days to decide whether to file it so that it can be reviewed. The FDA can refuse to file an application that is incomplete. For example, some required studies may be missing. In accordance with the Prescription Drug User Fee Act (PDUFA), the FDA's Center for Drug Evaluation and Research (CDER) expects to review and act on at least 90 percent of NDAs for standard drugs no later than 10 months after the applications are received. The review goal is six months for priority drugs. (See "The Role of User Fees.")

There is also continuous interaction throughout the review process. For example, over roughly six years, the sponsor Merck Research Laboratories of West Point, Pa., and the FDA had a half-dozen face-to-face meetings and about 28 teleconferences regarding the asthma drug Singulair (montelukast sodium).

"It's the clinical trials that take so long--usually several years," says Sandra Kweder, M.D., deputy director of the Office of New Drugs in CDER. "The emphasis on speed for FDA mostly relates to review time and timelines of being able to meet with sponsors during a drug's development," she says.

Reviewing Applications

Though FDA reviewers are involved with a drug's development throughout the IND stage, the official review time is the length of time it takes to review a new drug application and issue an action letter, an official statement informing a drug sponsor of the agency's decision.

Once a new drug application is filed, an FDA review team--medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts--evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. No drug is absolutely safe; all drugs have side effects. "Safe" in this sense means that the benefits of the drug appear to outweigh the risks.

The review team analyzes study results and looks for possible issues with the application, such as weaknesses of the study design or analyses. Reviewers determine whether they agree with the sponsor's results and conclusions, or whether they need any additional information to make a decision.

Each reviewer prepares a written evaluation containing conclusions and recommendations about the application. These evaluations are then considered by team leaders, division directors, and office directors, depending on the type of application.

Reviewers receive training that fosters consistency in drug reviews, and good review practices remain a high priority for the agency.

Sometimes, the FDA calls on advisory committees made up of outside experts, who help the agency decide on drug applications. Whether an advisory committee is needed depends on many things.

"Some considerations would be if it's a drug that has significant questions, if it's the first in its class, or the first for a given indication," says Mark Goldberger, M.D., director of one of CDER's drug review offices. "Generally, FDA takes the advice of advisory committees, but not always," he says. "Their role is just that -to advise."

Accelerated Approval

Traditional approval requires that clinical benefit be shown before approval can be granted. Accelerated approval is given to some new drugs for serious and life-threatening illnesses that lack satisfactory treatments. This allows an NDA to be approved before measures of effectiveness that would usually be required for approval are available.

Instead, less traditional measures called "surrogate endpoints" are used to evaluate effectiveness. These are laboratory findings or signs that may not be a direct measurement of how a patient feels, functions, or survives, but are considered likely to predict benefit. For example, a surrogate endpoint could be the lowering of HIV blood levels for short periods of time with anti-retroviral drugs.

Gleevec (imatinib mesylate), an oral treatment for patients with a life-threatening form of cancer called chronic myeloid leukemia (CML), received accelerated approval. The drug was also approved under the FDA's orphan drug program, which gives financial incentives to sponsors for manufacturing drugs that treat rare diseases. Gleevec blocks enzymes that play a role in cancer growth. The approval was based on results of three large Phase 2 studies, which showed the drug could substantially reduce the level of cancerous cells in the bone marrow and blood.

The sponsor, Novartis Pharmaceuticals Corp. of East Hanover, N.J., submitted the IND in April 1998. The FDA received the NDA in February 2001, and the drug was approved two-and-a-half months later in May 2001. Novartis has made commitments to conduct studies that confirm Gleevec's clinical benefit, such as increased progression-free survival in the treatment of CML .

Most drugs to treat HIV have been approved under accelerated approval provisions, with the company required to continue its studies after the drug is on the market to confirm that its effects on virus levels are maintained and that it ultimately benefits the patient. Under accelerated approval rules, if studies don't confirm the initial results, the FDA can withdraw the approval.

Because premarket review can't catch all potential problems with a drug, the FDA continues to track approved drugs for adverse events through a postmarketing surveillance program.

Bumps in the Road

If the FDA decides that the benefits of a drug outweigh the risks, the drug will receive approval and can be marketed in the United States. But if there are problems with an NDA or if more information is necessary to make that determination, the FDA may decide that a drug is "approvable" or "not approvable."

A designation of approvable means that the drug can probably be approved, provided that some issues are resolved first. This might involve the sponsor and the FDA coming to a final agreement on what

should go on the drug's labeling, for example. It could also involve more difficult issues, such as the adequacy of information on how people respond to various dosages of the drug.

A designation of "not approvable" describes deficiencies significant enough that it is not clear that approval can be obtained in the future, at least not without substantial additional data.

Common problems include unexpected safety issues that crop up or failure to demonstrate a drug's effectiveness. A sponsor may need to conduct additional studies--perhaps studies of more people, different types of people, or for a longer period of time.

Manufacturing issues are also among the reasons that approval may be delayed or denied. Drugs must be manufactured in accordance with standards called good manufacturing practices, and the FDA inspects manufacturing facilities before a drug can be approved. If a facility isn't ready for inspection, approval can be delayed. Any manufacturing deficiencies found would need to be corrected before approval.

"Sometimes a company may make a certain amount of a drug for clinical trials. Then when they go to scale up, they may lose a supplier or end up with quality control issues that result in a product of different chemistry," says the FDA's Kweder. "Sponsors have to show us that the product that's going to be marketed is the same product that they tested."

John Jenkins, M.D., director of CDER's Office of New Drugs, says, "It's often a combination of problems that prevent approval." Close communication with the FDA early on in a drug's development reduces the chance that an application will have to go through more than one cycle of review, he says. "But it's no guarantee."

The FDA outlines the justification for its decision in an action letter to the drug sponsor. When the action is either approvable or not approvable, CDER gives the sponsor a chance to meet with agency officials to discuss the deficiencies. At that point, the sponsor can choose to ask for a hearing, or correct any deficiencies and submit new information, or they can withdraw the application.

The Role of User Fees

Since the Prescription Drug User Fee Act (PDUFA) was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections. PDUFA has allowed the Food and Drug Administration to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process.

Under PDUFA, drug companies agree to pay fees that boost FDA resources, and the FDA agrees to time goals for its review of new drug applications. Along with supporting increased staff, drug user fees help the FDA upgrade resources in information technology. The agency has moved toward an electronic submission and review environment, now accepting more electronic applications and archiving review documents electronically.

The goals set by PDUFA apply to the review of original new human drug and biological applications, resubmissions of original applications, and supplements to approved applications. The second phase of PDUFA, known as PDUFA II, was reauthorized in 1997 and extended the user fee program through September 2002. PDUFA III, which extends to Sept. 30, 2007, was reauthorized in June 2002.

PDUFA III allows the FDA to spend some user fees to increase surveillance of the safety of medicines during their first two years on the market, or three years for potentially dangerous medications. It is during

this initial period, when new medicines enter into wide use, that the agency is best able to identify and counter adverse side effects that did not appear during the clinical trials.

In addition to setting time frames for review of applications, PDUFA sets goals to improve communication and sets goals for specific kinds of meetings between the FDA and drug sponsors. It also outlines how fast the FDA must respond to requests from sponsors. Throughout a drug's development, the FDA advises sponsors on how to study certain classes of drugs, how to submit data, what kind of data are needed, and how clinical trials should be designed.

The Quality of Clinical Data

The Food and Drug Administration relies on data that sponsors submit to decide whether a drug should be approved. To protect the rights and welfare of people in clinical trials, and to verify the quality and integrity of data submitted, the FDA's Division of Scientific Investigations (DSI) conducts inspections of clinical investigators' study sites. DSI also reviews the records of institutional review boards to be sure they are fulfilling their role in patient protection.

"FDA investigators compare information that clinical investigators provided to sponsors on case report forms with information in source documents such as medical records and lab results," says Carolyn Hommel, a consumer safety officer in DSI.

DSI seeks to determine such things as whether the study was conducted according to the investigational plan, whether all adverse events were recorded, and whether the subjects met the inclusion/exclusion criteria outlined in the study protocol.

At the conclusion of each inspection, FDA investigators prepare a report summarizing any deficiencies. In cases where they observe numerous or serious deviations, such as falsification of data, DSI classifies the inspection as "official action indicated" and sends a warning letter or Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) to the clinical investigator, specifying the deviations that were found.

The NIDPOE begins an administrative process to determine whether the clinical investigator should remain eligible to receive investigational products and conduct clinical studies.

CDER conducts about 300-400 clinical investigator inspections annually. About 3 percent are classified in this "official action indicated" category.

The FDA has established an independent Drug Safety Oversight Board (DSOB) to oversee the management of drug safety issues and communication to the public about the risks and benefits of medicines. The board's responsibilities include conducting timely and comprehensive evaluations of emerging drug safety issues, selecting drugs to be placed on a Drug Watch web site for health professionals and patients, and ensuring that experts--both inside and outside of the FDA--give their perspectives to the agency. The first meeting of the DSOB was held in June 2005.

For More Information

<http://www.fda.gov/cder/drug/DrugSafety/DSOBmeetings/>