

# From Idea to Market: The Drug Approval Process

Martin S. Lipsky, MD, and Lisa K. Sharp, PhD

---

**Background:** Each year many new prescription drugs are approved by the Food and Drug Administration (FDA). The process of developing and bringing new drugs to market is important for primary care physicians to understand.

**Methods:** We describe the drug development process based on a review of the literature and Web sites addressing FDA processes and policies.

**Results:** The process starts with preclinical testing. For drugs that appear safe, an investigational new drug application is filed with the FDA. If approved, clinical trials begin with phase 1 studies that focus on safety and pharmacology. Phase 2 studies examine the effectiveness of the compound. Phase 3 is the final step before submitting a new drug application (NDA) to the FDA. An NDA contains all the information obtained during all phases of testing. Phase 4 studies, or postmarketing studies, are conducted after a product is approved. Recent changes in legislation have streamlined the approval process. Critics contend that these changes have compromised public safety, resulting in the need to recall several products from the market. Proponents claim that changes in the approval process help patients with debilitating diseases, such as acquired immunodeficiency syndrome, that were previously denied critical medication because of bureaucratic regulations. (*J Am Board Fam Pract* 2001;14:362-7.)

---

The Food and Drug Administration (FDA) is responsible for assuring that foods and cosmetics are safe and that medicines and medical devices are both safe and effective. To carry out this responsibility, the FDA monitors more than \$1 trillion worth of products, representing about \$0.25 of every \$1.00 spent annually by American consumers.<sup>1</sup> Balancing the efficacy and safety of these products is the core public health protection duty of the FDA. This mission requires examining efficacy as determined from well-controlled trials, effectiveness as determined from actual use in uncontrolled settings, and safety for both prescription and over-the-counter pharmaceuticals before approving a medication for market. During the past decade alone, more than 500 new prescription drugs have been approved by the FDA.

Physicians face the continual challenge of learning about new products approved by the FDA. The process of developing new drugs and bringing new drugs to market has important practice implications yet is poorly understood by most primary care physicians. Understanding how clinical trials are conducted is important when physicians consider

the use of a new medication for patients in their own practices. For example, the medical literature or a pharmaceutical representative might refer to a phase 3 or phase 4 study. Table 1 provides a brief description of these terms and others used throughout this article. Understanding these terms will help the physician understand the risks involved in using a new medicine and the role of clinical trials in evaluating safety and effectiveness. Primary care physicians who might receive invitations to participate in clinical trials need to understand the risks involved for patients and the importance such investigations play in determining efficacy and safety issues of newly released medications. Finally, physicians who challenge the cost of new medications might benefit from a more complete understanding of the time, cost, and complex issues involved in having a new product approved by the FDA.

The purpose of this article is to present a concise overview of the drug approval process. It will briefly review the history of the FDA and follow the journey of a new product from early development until approval by the FDA for prescription use.

## Methods

We describe the drug development process based on a review of the literature and Web sites addressing FDA processes and policies. Key words used for the searches included "Food and Drug Administra-

---

Submitted, revised, 18 January 2001.

From the Department of Family Medicine (MSL, LKS), Northwestern University Medical School, Chicago. Address reprint requests to Martin S. Lipsky, MD, Department of Family Medicine, Morton 1-658, 303 East Chicago Ave, Chicago, IL 60611.

**Table 1. Terms and Definitions Relating to the New Drug Development Process.**

Term	Definition
Clinical evaluation, phase 1	Examines the pharmacologic actions and safe dosage range of a drug; how it is absorbed, distributed, metabolized, and excreted; and its duration of action
Clinical evaluation, phase 2	Controlled studies in volunteers to assess the effectiveness of a drug. Simultaneous animal and human studies can continue to examine further the safety of the drug
Clinical evaluation, phase 3	Testing using a greater number of volunteer patients. The drug is administered by practicing physicians to those suffering from the condition the drug is intended to treat. These studies must confirm earlier efficacy studies and determine low-incidence adverse reactions
Clinical evaluation, phase 4	Studies conducted after FDA approval, during general use of the drug by medical practitioners. Also referred to as postmarketing studies
Fast-track drugs	Fast-track approval provided for drugs that meet unmet medical needs for patients with serious or life-threatening conditions
Labeling	Any information distributed about a drug by the manufacturer, even if it is not physically affixed to the product. In addition to package inserts, labeling includes such material as advertising
Misbranding	Anything in labeling that is "false or misleading in any particular" renders the product misbranded, making it subject to FDA regulatory action

FDA - Food and Drug Administration.

tion," "drug development," and "drug approval." The databases searched were MEDLINE and CINAHL. Also, Web sites were sought using the Lycos search engine, and "Food and Drug Administration" and "drug approval" as key words.

### **FDA: A Historical Perspective**

Misfortune, disaster, and tragedy have triggered most of the advances in drug regulation. At the turn of the 19th century, the marketing of medicines was not controlled, and corruption, exploitation, and fraud were rampant. Public disclosures about the unsanitary conditions in meat-packing plants and concerns about worthless or even dangerous medicines led to the enactment of the Food and Drug Administration Act of 1906. This law (1) required that drugs meet official standards of strength and purity, (2) defined the terms *adulterated* and *misbranded*, and (3) prohibited the shipment for sale of misbranded and adulterated foods, drinks, and drugs.<sup>2-4</sup>

The FDA gained little power from this legislation, and it did not prevent the accidental deaths of 107 persons in 1937 from the patent medicine mar-

keted as "elixir sulfanilamide." A well-intentioned chemist used diethylene glycol as a solvent to make a liquid formulation of sulfanilamide that would be easier for children to take. Although the toxicity of diethylene glycol was known at the time, the manufacturer was not aware of it.<sup>5</sup> Existing law did not require that manufacturers demonstrate a drug's safety, and 240 gallons of the elixir were released into the marketplace.

As a consequence of this event, Congress enacted the Federal Food, Drug and Cosmetic Act of 1938, marking the birth of the modern FDA. The new act required that a manufacturer (not the FDA) prove the safety of a drug before it could be marketed, authorized factory inspections, and established penalties for fraudulent claims and misleading labels. Following the 1938 Act, the FDA began to distribute public notices (known as trade correspondences) to the industry regarding the labeling and dispensing of drugs. It was in these public notices that the FDA first distinguished medications that should be available only by prescription.<sup>3</sup> Specifically it required that all drugs either carry a label with adequate information for

consumer use or a caution label. The caution label warned consumers that the drug should be used only by or on prescription of a physician.

At this point the decision about which drugs should receive a caution label was largely at the discretion of the manufacturer. In 1951, the Durham-Humphrey Amendment set forth the basis for distinguishing between prescription and nonprescription drugs. The amendment specified that three classes of drug be available by prescription: habit-forming drugs, drugs considered unsafe for use except under expert supervision because of toxicity or other potential harmful effects, and drugs limited to prescription use only under a manufacturer's new drug application.<sup>4</sup>

In 1961, an Australian obstetrician, William McBride, reported an increase of fetal malformations in association with the hypnotic drug thalidomide. Although thalidomide was heavily marketed in Western Europe, approval of this drug was delayed by the FDA in the United States and never made it to market. This near catastrophe, however, highlighted the need for more stringent laws, and in 1962, Congress passed the Kefauver-Harris Amendment. This act not only required that manufacturers prove to the FDA that a drug is safe but, for the first time, required that the manufacturer provide evidence that the product was effective for the claims made in labeling.<sup>6</sup> Effectiveness needed to be established through adequate and well-controlled investigations by qualified researchers.

In the late 1970s there was concern about the quality of scientific data submitted to the FDA. This concern led to the establishment of good laboratory practices and guidelines for clinical trials to assure the quality and integrity of the safety data filed with the FDA. Important elements of the guidelines included the qualifications of the investigator, the study facilities, study management, safeguards for the safety and rights of patients, adherence to the research protocol, record keeping, and study monitoring. Many of these guidelines have now become regulation, such as the need to provide informed consent and the basic elements of informed consent, and essentially spell out the requirements for institutional review boards (IRBs).<sup>7</sup>

In 1987, partially in response to the human immunodeficiency virus (HIV) epidemic, new regulations were developed to accelerate approval for high-priority medications. Before then, drugs were approved based on their effect on the illness or on

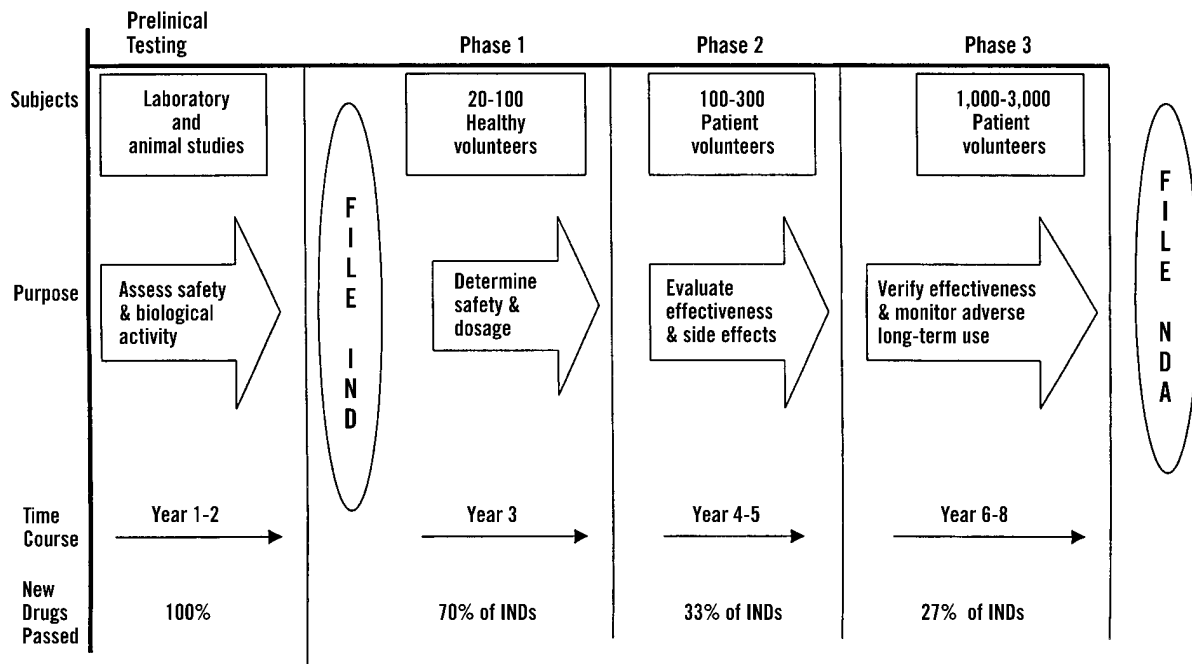
survival. Accelerated approval allowed the FDA to judge drugs using a surrogate endpoint, or the effect of the drug on a physiologic process or marker associated with a disease. For example, CD4 cell counts could be used to measure the effectiveness of an antiviral medication in treating HIV-infected patients. This new standard allowed the FDA to approve a promising drug without completing a full clinical trial.<sup>6</sup>

## Drug Development

Drug development can generally be divided into phases. The first is the preclinical phase, which usually takes 3 to 4 years to complete. If successful, this phase is followed by an application to the FDA as an investigational new drug (IND). After an IND is approved, the next steps are clinical phases 1, 2, and 3, which require approximately 1, 2, and 3 years, respectively, for completion (Table 1). Importantly, throughout this process the FDA and investigators leading the trials communicate with each other so that such issues as safety are monitored. The manufacturer then files a new drug application (NDA) with the FDA for approval. This application can either be approved or rejected, or the FDA might request further study before making a decision. Following acceptance, the FDA can also request that the manufacturer conduct additional postmarketing studies. Overall, this entire process, on average, takes between 8 to 12 years.<sup>2</sup> Figure 1 summarizes the drug approval process.

It is not surprising that from conception to market most compounds face an uphill battle to become an approved drug. For approximately every 5,000 to 10,000 compounds that enter preclinical testing, only one is approved for marketing.<sup>8</sup> A 1993 report by the Congressional Office of Technology Assessment estimated the cost of developing a new drug to be \$359 million.<sup>9</sup> Newer figures place the cost at more than \$500 million.<sup>10</sup>

The first step, a preclinical phase, is to find a promising agent, which involves taking advantage of the advances made in understanding a disease, pharmacology, computer science, and chemistry. Breaking down a disease process into its components can provide clues for targeting drug development. For example, if an enzyme is determined to be a key component of a disease process, a researcher might seek ways to inhibit this enzyme.



**Figure 1. Overview of drug development process and review. IND - investigational new drug, NDA - new drug application. Adapted from: The Drug Development Approval Process. Available at <http://www.phrma.org/charts/approval.html>.**

Advances in basic science might help by ascertaining the active enzyme site. Numerous compounds might be synthesized and tested before a promising agent emerges. Computer modeling often helps select what compounds might be the most promising.

The next step before attempting a clinical trial in humans is to test the drug in living animals, usually rodents. The FDA requires that certain animal tests be conducted before humans are exposed to a new molecular entity. The objectives of early in vivo testing are to demonstrate the safety of the proposed medication. For example, tests should prove that the compound does not cause chromosomal damage and is not toxic at the doses that would most likely be effective. The results of these tests are used to support the IND application that is filed with the FDA. The IND application includes chemical and manufacturing data, animal test results, including pharmacology and safety data, the rationale for testing a new compound in humans, strategies for protection of human volunteers, and a plan for clinical testing.<sup>2,9</sup> If the FDA is satisfied with the documentation, the stage is set for phase 1 clinical trials.

Phase 1 studies focus on the safety and pharmacology of a compound.<sup>11</sup> During this stage low

doses of a compound are administered to a small group of healthy volunteers who are closely supervised. In cases of severe or life-threatening illnesses, volunteers with the disease may be used. Generally, 20 to 100 volunteers are enrolled in a phase 1 trial. These studies usually start with very low doses, which are gradually increased. On average, about two thirds of phase 1 compounds will be found safe enough to progress to phase 2.

Phase 2 studies examine the effectiveness of a compound. To avoid unnecessarily exposing a human volunteer to a potentially harmful substance, studies are based on an analysis of the fewest volunteers needed to provide sufficient statistical power to determine efficacy. Typically, phase 2 studies involve 100 to 300 patients who suffer from the condition the new drug is intended to treat. During phase 2 studies, researchers seek to determine the effective dose, the method of delivery (eg, oral or intravenous), and the dosing interval, as well as to reconfirm product safety.<sup>2,7,11,12</sup> Patients in this stage are monitored carefully and assessed continuously. A substantial number of these drug trials are discontinued during phase 2 studies. Some drugs turn out to be ineffective, while others have safety problems or intolerable side effects.

Phase 3 trials are the final step before seeking FDA approval. During phase 3, researchers try to confirm previous findings in a larger population. These studies usually last from 2 to 10 years and involve thousands of patients across multiple sites. These studies are used to demonstrate further safety and effectiveness and to determine the best dosage. Despite the intense scrutiny a product receives before undergoing expensive and extensive phase 3 testing, approximately 10% of medications fail in phase 3 trials.

If a drug survives the clinical trials, an NDA is submitted to the FDA. An NDA contains all the preclinical and clinical information obtained during the testing phase. The application contains information on the chemical makeup and manufacturing process, pharmacology and toxicity of the compound, human pharmacokinetics, results of the clinical trials, and proposed labeling. An NDA can include experience with the medication from outside the United States as well as external studies related to the drug.

After receiving an NDA, the FDA completes an independent review and makes its recommendations. The Prescription Drug User Fee Act of 1992 (PDUFA) was designed to help shorten the review time. This act allowed the agency to collect user fees from pharmaceutical companies as financial support to enhance the review process. The 1992 act specifies that the FDA reviews a standard drug application within 12 months and a priority application within 6 months. Application for drugs similar to those on the market are considered standard, whereas priority applications represent drugs offering important advances in addition to existing treatments. If during the review the FDA staff feels there is a need for additional information or corrections, they will make a written request to the applicant. During the review process it is not unusual for the FDA to interact with the applicant staff.<sup>12</sup>

Once the review is complete, the NDA might be approved or rejected. If the drug is not approved, the applicant is given the reasons why and what information could be provided to make the application acceptable. Sometimes the FDA makes a tentative approval recommendation, requesting that a minor deficiency or labeling issue be corrected before final approval. Once a drug is approved, it can be marketed.

Some approvals contain conditions that must be met after initial marketing, such as conducting additional clinical studies. For example, the FDA might request a postmarketing, or phase 4, study to examine the risks and benefits of the new drug in a different population or to conduct special monitoring in a high-risk population. Alternatively, a phase 4 study might be initiated by the sponsor to assess such issues as the longer term effects of drug exposure, to optimize the dose for marketing, to evaluate the effects in pediatric patients, or to examine the effectiveness of the drug for additional indications.<sup>7</sup> Postmarketing surveillance is important, because even the most well-designed phase 3 studies might not uncover every problem that could become apparent once a product is widely used. Furthermore, the new product might be more widely used by groups that might not have been well studied in the clinical trials, such as elderly patients. A crucial element in this process is that physicians report any untoward complications. The FDA has set up a medical reporting program called Medwatch to track serious adverse events (1-800-FDA-1088). The manufacturer must report adverse drug reactions at quarterly intervals for the first 3 years after approval,<sup>10</sup> including a special report for any serious and unexpected adverse reactions.

### Recent Developments in Drug Approval

The Food and Drug Administration Modernization Act of 1997 (FDAMA) extended the use of user fees and focused on streamlining the drug approval process.<sup>11,13</sup> In 1999, the 35 drugs approved by the FDA were reviewed in an average of 12.6 months, slightly more than the 12-month goal set by PDUFA.<sup>10</sup> This act also increased patient access to experimental drugs and facilitated an accelerated review of important new medications. The law ended the ban on disseminating information to providers about non-FDA-approved uses of medications. A manufacturer can now provide peer-reviewed journal articles about an off-label indication of a product if the company commits to filing a supplemental application to establish the use of the unapproved indication. As part of this process, the company must still conduct its own phase 4 study. As a condition for an accelerated approval, the FDA can require the sponsor to carry out post-marketing studies to confirm a clinical benefit and product safety.



# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.