

Introduction to Drug Development and FDA Drug Approval Processes

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Introduction

The process for obtaining approval from the U.S. Food and Drug Administration (FDA) to market a new drug takes many years, many millions of dollars, many experts, and many study subjects. The purpose of this article is to explain the basics of the drug development and FDA approval processes.

The FDA is part of the U.S. Department of Health & Human Services (DHHS). Within the FDA, the Center for Drug Evaluation and Research (CDER) is responsible for non-biological pharmaceuticals (typically "small molecules"). The Center for Biologics Evaluation and Research (CBER) is responsible for biological drugs (typically "large molecules"), vaccines and blood-based products. The two Centers operate in a similar fashion, although there are distinct differences that are beyond the scope of this article, which will focus on CDER. Other FDA centers are responsible for other types of medical products, as well as foods and cosmetics.

The FDA does not, itself, test new drugs. Instead, pharmaceutical companies generate and compile data for review by a team of FDA experts¹.

The Drug Development Process¹

Drug Discovery⁴

The objective in drug discovery is to identify molecules with the potential to become drugs. Scientists can test a likely molecule in a test tube or screen libraries of thousands or even millions of molecules with robotic lab equipment. In some cases, scientists work backwards from a property of the disease, e.g., a defective enzyme, to deduce what an effective drug might look like, and then find or create a molecule with the necessary characteristics.

Only a tiny fraction of drug candidates make it through the entire process to become pharmaceuticals. And then, even some that are approved for marketing are later found to be deficient and withdrawn from the market. It is therefore essential to concentrate drug development resources on the very best candidates.

Preclinical Testing^{4,5}

In preclinical testing, drug candidates are first tested with living cells and tissues. For FDA approval, new drugs must be tested in two or more species of live animals, typically a rodent and another species that resembles humans in the relevant organ(s) and physiological process(es). Primates are obvious candidates, but are very expensive, raise the most serious ethical issues, and may not be the best choice scientifically. If possible, the drug is tested on animals with the same medical condition that potential human patients will have. Some laboratory animals are genetically engineered for this purpose. No matter the species, preclinical testing is far from perfect in predicting a drug's usefulness in humans.

It is especially important to understand toxicity before any testing in humans. Experiments determine the pharmacokinetic properties of absorption, distribution, metabolism and excretion (ADME) and physiological (pharmacodynamic) properties of the drug. Formulation

scientists help determine the best delivery system, e.g., oral, time-release, topical or intravenous, to optimize these properties.

The Investigational New Drug Application (IND)¹⁻⁴

With preclinical data in hand, the pharmaceutical company can decide whether to ask the FDA for approval to test the drug on humans. If it decides to proceed, it files an Investigational New Drug Application (IND) with the FDA. The IND includes three main sections: Animal Pharmacology & Toxicology Studies, Manufacturing Information, and Clinical Protocols & Investigator Information. From a legal perspective, IND approval exempts the drug from the FDA's rule against transportation of unapproved drugs across state lines.

Clinical trials proceed in a three-phase process that exposes more and more people to the drug as its safety and effectiveness become better understood. The eventual goal is to create data that will prove to the FDA that the drug is safe and effective, i.e., has an acceptable risk/benefit profile. Numerous studies are often conducted across the three phases. (See Table 1.)

Table 1. Drug Clinical Trial Phases

	Timelines^a	Number of Subjects^b	Success Rates^c
Phase I	~1 - 2 years	~20 - 100	71% to Phase II
Phase II	~2 - 3 years	~20 - 300	45% to Phase III
Phase III	~2 - 3 years	~300 - 3000 or more	64% to NDA submission, 93% of which are approved

- a. Tufts Center for the Study of Drug Development, 2006
- b. "Clinical trial," Wikipedia, accessed June 27, 2011 at http://en.wikipedia.org/wiki/Clinical_trial#Phases
- c. Tufts Center for the Study of Drug Development, 2010; 19% of drugs that enter Phase I obtain FDA marketing approval

Phase I Clinical Trials¹⁻⁵

In Phase I trials, the new drug is tested on humans, so safety requirements are far more stringent than in preclinical trials (at the end of which, the animals might be "sacrificed" to observe the drug's effects.) Phase I study subjects are typically healthy, so effectiveness cannot be evaluated. Healthy subjects gain no health benefits, amplifying safety concerns. (Phase I cancer trials usually employ cancer patients because the drugs are so toxic, and receive too little treatment to gain health benefits.)

In a common Phase I study design — dose escalation—the dosage increases from subject to subject until toxicity or some other issue appears. Data is collected on drug toxicity/tolerability, pharmacokinetics and pharmacodynamics to determine the most likely dosing and mode of administration for Phase II trials. However, development will stop for a myriad of possible reasons, such as the drug being too toxic or impractical to formulate effectively.

Phase II Clinical Trials¹⁻⁵

In Phase II trials, the new drug is tested on people with the medical condition of interest. Safety is still an issue, but effectiveness now becomes important. Data collected in Phase II studies are used to design Phase III studies. A common Phase II design — dose ranging —

attempts to determine the dosage with the best balance of safety and effectiveness. Phase II studies can also identify the best subject population for Phase III.

Phase III Clinical Trials¹⁻⁵

Phase III studies test the drug for safety and effectiveness. The primary objective is to create two “pivotal” studies that prove the drug market-worthy to the FDA. Phase III studies use much larger subject populations than previous phases, increasing their cost substantially and potentially revealing relatively rare safety issues.

The New Drug Application (NDA)^{1-3,5}

The FDA evaluates the safety and effectiveness of new drugs. (It does not consider the eventual price that the pharmaceutical company will charge for the drug.) The benefits of the drug must outweigh its risks. For example, the FDA will approve a life-saving cancer drug with dangerous side effects but that would be unacceptable for a wrinkle cream. The FDA is relatively more likely to approve a new drug that has a better benefit/risk profile than drugs already on the market, but has no objection to “me too” drugs *per se*. One reason there are so many “me too” drugs available is that they often offer different benefit/risk profiles to different patients. These differences might not appear until after the new drug is on the market.

FDA reviewers obtain advice from advisory committees like the Oncologic Drugs Advisory Committee (ODAC). These committees are composed of physicians, pharmacologists, scientists and other experts. At least one member should bring a consumer perspective.

Assuming Phase III studies generate positive results, the pharmaceutical company compiles and analyzes all the data from preclinical testing and clinical trials, manufacturing details, and other information in an NDA, which it submits to the FDA. NDAs are now submitted in electronic form, but in paper form, some of them could fill a tractor-trailer truck.

Ideally, the NDA presents an overwhelmingly persuasive case for approval of the drug. However, human physiology and diseases are complicated, so the NDA will probably have to explain suspicious safety issues, ambiguities in the results, weaknesses in the data, creative statistical methods, or other factors that require a judgment call by the FDA. The FDA approves an NDA provided it finds these explanations persuasive.

In addition to safety and effectiveness, the FDA must also approve the pharmaceutical company's proposed drug labeling (package insert) and agree that the company's plans for manufacturing the drug ensure its identity, strength, quality and purity.

Phase IV (Post-Marketing) Clinical Trials^{1,2,5}

The FDA also monitors the safety of marketed drugs. Because rare side effects might not become apparent until a drug is on the market, the FDA increasingly requires post-marketing “commitment studies” when it approves a drug for marketing. Pharmaceutical companies also conduct Phase IV studies to learn more about its marketed drugs. However, clinical trials intended to support changes in the label of a marketed drug, e.g., for a new indication, population or dosage, are considered Phase III trials.

Expanded Access²

Clinical development (the clinical trial process) takes years and is limited to a tiny fraction of the people who might benefit when a new drug is eventually approved. Some drugs under development show promise for treating patients with serious or immediately life-threatening

diseases, or conditions lacking other therapeutic options. Imagine a child who is too ill to qualify for a clinical trial and is likely to die before the drug reaches the market. In the absence of other treatment options, why not try the new drug?

The FDA has therefore established “Expanded Access” mechanisms to make such drugs available under limited conditions. Initially, these mechanisms were characterized as “compassionate use of investigational products.” More recently, the FDA has created more-formal programs: Group C (Treatment) INDs, Parallel Track (Treatment) Protocols, and Emergency Use INDs.

Under these programs, individual patients and even groups of patients can gain access to unapproved drugs as if they were participating in clinical trials. Larger groups require more evidence of the drug’s safety and potential efficacy. Most expanded access trials follow the normal processes for protection of human subjects in clinical trials, including informed consent and Institutional Review Board (IRB) approval of a streamlined protocol. The FDA is more likely to approve expanded access INDs and protocols after the drug reaches Phase III trials.

Group C (Treatment) INDs²

Group C (Treatment) INDs program are intended for seriously ill patients that meet two conditions: (a) there are no acceptable treatments available with approved drugs and (b) the risks of taking the unapproved drug are outweighed by the possible benefits. Also, the pharmaceutical company must be willing to make the drug available free of charge. In addition to the possible benefits to the patient, the FDA and the pharmaceutical company can gain useful information from real-world use outside the controlled parameters of a clinical trial.

Parallel Track (Treatment) Protocols^{1,2}

In 1992, HIV/AIDS advocacy groups persuaded the FDA to create Parallel Track (Treatment) Protocols because large numbers of HIV/AIDS patients were dying while the initial drugs were winding their way through clinical development and FDA approval. (However, not all of these drugs proved to be safe and effective.) Parallel Track Protocols typically are not randomized, blinded or controlled (i.e., compared to a placebo or other drug), but they do generate useful data on matters like disease progression and survival rates.

Emergency Use INDs¹

In an emergency situation, a physician might conclude that he or she has no choice but to administer an unapproved drug immediately, without waiting for an IND or IRB approval. The physician might have the drug in stock for an ongoing study, or ask the pharmaceutical company to provide it. The FDA requires reporting of such “studies” to both the FDA and the IRB as soon as possible. For obvious reasons, Emergency Use INDs are used sparingly.

Expedited Availability⁶

While Expanded Access programs make experimental drugs available while they are in clinical development, Expedited Availability programs are intended to accelerate the clinical development and approval process for drugs that are the first available treatment for a disease or indication, or have significant advantages over existing therapies. The FDA has developed three programs for Expedited Availability: Accelerated Approval, Priority Review, and Fast Track (Subpart E). Pharmaceutical companies with promising new drugs can apply for these programs. (See Table 2.)

Table 2. FDA Expedited Availability Programs

	Fast Track	Accelerated Review	Priority Review
Authority	FFDCA 506(a).	21 CFR 314 and 601 (1992). FFDCA 506(b) (1997)	CDER MAPP 6020.3 and CBER SOPP 8405 (1996)
Qualifying Criteria	Serious or life-threatening condition	Serious or life - threatening condition	n/a
	Potential to address unmet medical need	Potential to address unmet medical need	Major advance in treatment or treatment where no adequate therapy exists
	n/a	Adequate and well-controlled studies supporting use of surrogate outcome	n/a
Benefit during development	Close communication with FDA	Adjusted trial outcome requirements	n/a
Benefit during review	Rolling review or priority review	n/a	Additional attention; expedited review
Postapproval requirement	n/a	Studies to extend results from surrogate to clinical outcome	n/a

Source: "FDA Fast Track and Priority Review Programs," Susan Thaul, Congressional Research Service, 2008, <http://www.nationalaglawcenter.org/assets/crs/RS22814.pdf>

Accelerated Approval^{2,6}

The Accelerated Approval program allows the FDA to approve drugs based on surrogate endpoints. A surrogate endpoint is a biological marker that predicts clinical benefit but is not the clinical benefit itself. For example, a reduction in viral load, tumor size, or blood cholesterol should (but not always does) predict higher survival rates. Because these surrogate endpoints appear sooner than the clinical benefit, clinical trials can be faster. Accelerated Approval is conditional on confirmation of actual clinical benefit through well-controlled Phase IV studies. The FDA can withdraw approval if confirmatory trials do not show clinical benefit.

Priority Review^{1,2,5,6}

The 1992 Prescription Drug User Fee Act (PDUFA) mandated the FDA to complete Standard Reviews of NDAs within 10 months and Priority Reviews within six months. The FDA should

grant or deny Priority Review status within 45 days for drugs that evidence significant advances in treatment, such as the following:

- Increased effectiveness, prevention or diagnosis of a disease
- Elimination or substantial reduction of a treatment-limiting drug reaction
- Enhancement of patient willingness or ability to take the drug according to the required schedule and dose
- Safety and effectiveness in a new population like children

The FDA does not require that the drug treat a serious disease. Priority Review status does not affect the rigor of FDA's NDA review or the drug's clinical development program, only the applicant's place in FDA's NDA review queue.

Fast Track (Subpart E)^{5,6}

The FDA grants Fast Track (Subpart E) status to investigational drugs that show enough promise in filling unmet needs for treating serious illnesses or underserved therapeutic areas. A pharmaceutical company can request Fast Track status at any time during the drug development process. The FDA should grant or deny Fast Track status within 60 days.

Fast Track status makes a drug eligible for some or all of the following advantages:

- More frequent meetings with the FDA to discuss the drug's development plan and ensure collection of data the FDA will need to approve the drug.
- Frequent written correspondence with the FDA about study design
- Eligibility for Accelerated Approval and Priority Review
- Eligibility for Rolling Reviews, in which the FDA reviews completed sections of the NDA as they are completed
- Access to a dispute resolution system if the pharmaceutical company is not satisfied with an FDA decision. [Questions: What kind of decisions? Are these features available only to Fast Track drugs?]

Orphan Drugs^{5,7,8}

The FDA grants Orphan Drug status to drugs intended to treat rare diseases and conditions (fewer than 200,000 patients in the U.S) for which the costs of drug development cannot reasonably be recovered by drug sales in the U.S. Pediatric patients are considered "therapeutic orphans" due to inadequate pediatric dosing information on marketed drugs, so expanding a drug's label to children qualifies a drug for Orphan Drug status with pediatrics patients. Most Orphan Drugs qualify for Priority Review, as well as significant other benefits. However, they are still subject to normal clinical trial regulations and NDA requirements.

Off-Label Use²

The FDA does not regulate the practice of medicine. In other words, physicians are generally free to prescribe approved drugs for "off label" use by any patient with any medical condition at any dosage, subject to medical ethics, insurance reimbursement policies, and potential malpractice litigation. As a result, potential subjects for Phase IV studies can obtain the same drugs in a personalized regime tailored by their physician, provided they can afford the medicine.

Investigator Initiated INDs¹

Industry-sponsored clinical trials are sponsored by a pharmaceutical company, which files the IND, and conducted by one or more investigators. It is also possible for an investigator to file the IND and take on the sponsor's responsibilities in the study. (The pharmaceutical company normally provides the study drug and often provides funding for the trial.) These trials are commonly known as Investigator-Initiated trials (IITs), among other names. IITs usually explore off-label uses of approved drugs. They are subject to all the same regulations as industry-sponsored trials.

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