



Primer: Introduction to the FDA Drug Approval Process and Off Label Use

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Introduction

The United States is home to the majority of the world's new drug developers. With this rapidly expanding industry constantly offering Americans new health care treatments, Congress passed legislation at the turn of the 20th century to protect citizens from “quackery” and ensure the safety and effectiveness of all new pharmacological treatments. Since then the Food and Drug Administration (FDA) has expanded rapidly and become a major influence on the pharmaceutical industry.

The FDA Drug Approval Process

Since the passage of the Food, Drug, and Cosmetics Act (FDCA), the FDA has an increasingly large role in approving products intended for human consumption. Drug approvals specifically are managed by the Center for Drug Evaluation and Research (CDER).^[1] The CDER must examine and approve all applications for new molecule entities (novel drug compounds), generic drugs, and over the counter (OTC) drugs. It takes these products, on average, about 10 years from discovery to reach the market.^[2]

Once a new drug is discovered, there is a specific series of steps it must go through to acquire FDA approval. Before any applications are sent to the FDA, the drug developer must run pre-clinical laboratory tests, typically using animal samples, to rule out any significant adverse effects.^[3] This process takes 3 years on average. Only 1 in 1,000 drugs will make it past this stage.^[4]

After pre-clinical testing is finished, an Investigational New Drug (IND) application must be submitted to the FDA/CDER explaining the results of previous trials, how new studies will be conducted, how volunteer subjects will be chosen, the chemical structure of the new drug, how it is believed to work within human biochemistry, how it is manufactured, and any known or anticipated side effects.^[5] If this application is not rejected within 30 days, it is considered approved. If approved, any clinical trials that are carried out must first be submitted to and approved by an Institutional Review Board (IRB)—a group of scientists, academics, and subject matter experts approved by the Department of Health and Human Services (HHS) who approve and oversee experiments done on human subjects to ensure they are performed ethically.^[6]

Phase I clinical trials involve a small sample group of 30-80 typically healthy volunteers. The purpose is to determine safe dosages, absorption rates, duration of the drug's effects, and any side effects. This stage typically takes about 1 year.^[7]

If Phase I trials show the drug to be relatively safe, Phase II trials begin. These involve 100-300 patients and controlled studies to test minimum and maximum dosages and their effectiveness. This stage takes an additional 2 years.[\[8\]](#)

The final stage of pre-market testing, Phase III, is a randomized, controlled study of 1,000-3,000 patients testing safety and effectiveness of the drug. This process takes approximately 3 years.[\[9\]](#)

Once clinical testing has finished, the drug developer must submit a New Drug Application (NDA) including all relevant data and information about the drug – these applications often reach 100,000 pages. Approval or denial of these applications currently takes an average of 12 months. An NDA may be denied with explanation, approved outright, or approved on the condition that the manufacturer makes minor changes, such as labeling adjustments.[\[10\]](#)

All drugs with NDAs that make it to market are subject to Phase IV, or post-marketing studies, to track the voluntary reporting of adverse side effects. Less than 3 percent of approved drugs are ever recalled based on Phase IV reporting.[\[11\]](#)

Speeding Up the Process

Speeding up the process of drug approvals has been a major concern for pharmaceutical companies and patient advocacy groups, particularly since the beginning of the AIDS epidemic in the 1980's. Since then, several approaches to fast-tracking access to new drugs have emerged.

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA), which requires drug companies submitting new drugs (and biologics) for FDA approval to pay a fee to support the CDER specifically; providing additional resources to facilitate faster drug approval.[\[12\]](#) Fees are also applied to up to 2 years of post-marketing studies of approved drugs to aid in quality control. PDUFA has been widely considered a success. As a compromise between companies paying the fees and the FDA, the CDER has used PDUFA funds to decrease the average approval time of NDAs from 30 months to 12 months. Since PDUFA's reauthorization in 2012, CDER has a new goal to lower the average approval time to 10 months for a standard NDA.[\[13\]](#)

There is another PDUFA-related drug approval fast track for priority drugs that treat orphan diseases, rapidly spreading diseases with no other effective treatment, chronic or widespread illnesses with no more effective treatment alternative, and qualified antibiotics.[\[14\]](#) Fast-track approval provides drug companies with the opportunity for more frequent communication with the FDA regarding trial design and data collection, priority review, and rolling submission of NDA materials as they become available. Under PDUFA, priority review drugs typically receive a decision from CDER within 6 months of submission.[\[15\]](#)

Compassionate Use programs (also known as Right to Try) occasionally allow terminally ill individuals to try an experimental drug that is still going through clinical trials if the drug has been through Phase I and is not considered dangerous.

Post Approval Use of Drugs

Once a drug is approved by the FDA for any indication, its prescription and use is then left to the discretion of health care providers' medical and ethical judgments. Off-label drug use is common and includes any use that is different from the intended and labeled indication, dose, mode of administration, patient age or gender, or

duration of use.[16]

Although up to 70 percent of off-label drug use lacks scientific backing,[17] it is still incredibly prevalent, and in some cases an off-label use may even become the primary reason a drug is prescribed.[18] For example, pediatric antipsychotic drugs are prescribed off-label over 77 percent of the time.[19] Off-label use is especially common among specialties where patients are rare or unable to give consent, therefore making it difficult to secure a large enough volunteer base to run clinical trials. For example, oncology, pediatrics, geriatrics, and obstetrics all rely heavily on off-label drug uses.[20]

At first, drug manufacturers were prohibited from promoting a drug's off-label uses by the FDA. However, through the FDCA Congress has allowed drug companies to distribute "enduring materials" such as peer-reviewed journals which discuss off-label use under certain conditions including a promise to seek FDA approval.[21]

Economic factors may discourage drug companies from seeking FDA approval. In many instances the patient population for off-label use is too small to produce statistically significant results, or to justify their expense for a drug whose exclusivity period is already running. To address this, Congress has granted an extension of exclusivity where a new use is approved, but this is not guaranteed to recover trial costs, nor is the new approval itself guaranteed.[22]

In the 1990's, federal courts further expanded drug manufacturers' interests in off-label uses by holding that promoting off-label uses is a constitutionally protected right, but that the company's financial interest and lack of FDA approval must be disclosed.[23] Subsequent FDA guidance has attempted to better delineate the extent to which knowledge of off-label drug use may be promoted. That guidance, though on questionable constitutional ground, has not yet been challenged in the courts.

[1] <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082585>.