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## **The U.S. Drug Approval Process: A Primer**

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# The U.S. Drug Approval Process: A Primer

## Summary

Drug approval standards in the United States are considered by many to be the most demanding in the world. By law, all new drugs must first be shown to be safe and effective before they can be approved by the Food and Drug Administration (FDA) for marketing. While these requirements are considered the norm today, it took a century of law and rulemaking before they became the nation's gold standard. Up until the early part of the last century, the sale of adulterated and misbranded drugs was not uncommon until the practice was outlawed under the 1906 Food and Drugs Act. Thirty years later, Congress passed the Federal Food, Drug, and Cosmetic Act of 1938, that required drug companies to conduct pre-market safety testing before their new drug could be marketed. In 1962, following the infamous thalidomide tragedy, Congress amended the law once again, this time adding the requirement that manufacturers prove the effectiveness of their products, as well.

Discovering a new drug, and shepherding it through FDA's review process, can take many years, and cost hundreds of millions of dollars. To a large degree, these costs are mostly associated with the clinical testing that must be done to convince the agency that the new product is safe and effective for its intended medical use. To begin clinical testing, drug companies or sponsors must file an Investigational New Drug (IND) application with the FDA. The INDs must include information about the study protocol, the qualifications of the lead investigator, the trial's location, and assurances that the welfare of the study participants will be protected.

Once a new drug's clinical testing is complete, the sponsor submits a New Drug Application (NDA) for FDA evaluation. During the application's review, agency officials examine the drug's safety and efficacy data, assay samples, and conduct factory inspections to be sure the finished product will be manufactured properly. FDA also checks the drug's labeling to be sure that it is accurate and comprehensive. Typically, when FDA finishes its review, it notifies the applicant by letter stating that its NDA is either approved, would be approved if changes are made, or cannot be approved due to unresolved problems. Once a new drug is approved, its safety is monitored through FDA's post-marketing surveillance system, MedWatch. By regulation, manufacturers must report all serious adverse reactions. However, for health professionals and consumers, reporting adverse reactions is voluntary.

During the 1990s, Congress adopted several measures aimed at accelerating the drug approval system. In 1992, it passed the Prescription Drug User Fee Act, which authorized FDA to collect fees from companies in order to speed up NDA review. Five years later, Congress enacted the Food and Drug Administration Modernization Act of 1997 (FDAMA), the most comprehensive overhaul of the nation's food, drug, and medical device laws in more than 30 years. Among its provisions related to the drug approval process, FDAMA streamlined clinical testing requirements, expanded patients' access to experimental drugs, and granted pharmaceutical companies extra marketing exclusivity for determining the use of their products in pediatric patients. FDAMA also eased data reporting requirements, and modified the law so fewer clinical studies are required to confirm a drug's effectiveness.

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# The U.S. Drug Approval Process: A Primer

## Historical Background

The United States has perhaps the world's most stringent standards for approving new drugs. These standards, and the statutes that support them, evolved slowly during the past century as lawmakers strove to keep pace with advances in pharmacology, and growing consumer demand for safer drugs. Until early in the twentieth century, there were no federal laws requiring drug manufacturers to verify the quality of the medicinals they sold in America. Untested remedies and popular cure-alls were widely sold, most with no assurance of their quality, safety, or medical benefit. Growing increasingly skeptical of the burgeoning patent medicine trade, health advocates in the early 1900s began pressing for reforms that would give consumers some protection from the growing number of unproven health claims appearing in product advertising and labeling.<sup>1</sup> In response to these concerns, Congress passed the Food and Drugs Act of 1906.<sup>2</sup> While the new law prohibited manufacturers from introducing misbranded and adulterated foods and drugs into interstate commerce, it did not require pharmaceutical companies to prove that their drugs were safe.

Following the infamous “elixir of sulfanilamide” incident,<sup>3</sup> where more than 100 patients died from taking a drug containing a poisonous solvent, Congress passed the Federal Food, Drug, and Cosmetic Act (FD&C Act) of 1938.<sup>4</sup> Besides adding new quality standards for both food and drugs, the law, for the first time, required drug manufacturers to provide evidence that their products were safe before they could be approved by the U.S. Food and Drug Administration (FDA) for marketing.

A call for revamping the nation's drug laws came again in the early 1960s when the world learned that thalidomide, a new drug being taken by pregnant women to treat morning sickness, was responsible for birth defects in thousands of babies born in western Europe.<sup>5</sup> Thalidomide's approval was pending in the United States at that time, but an FDA drug reviewer had serious reservations about the drug's safety.

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<sup>1</sup>Janssen, Wallace F. Pharmacy ... and the Food and Drug Law. A Significant Relationship. *American Pharmacy*, v. NS21, no. 4, April 1981, p. 30.

<sup>2</sup>Food and Drugs Act, Pub. L. no. 384, ch. 3915, 34 stat. 768 (1906).

<sup>3</sup>FDA Backgrounder. *Milestones in U.S. Food and Drug Law History*. May 3, 1999. [<http://www.fda.gov/opacom/backgrounders/miles/html>].

<sup>4</sup>Federal Food, Drug, and Cosmetic Act, Pub. L. no. 717, 52 stat. 1040 (1938).

<sup>5</sup>Grigg, William. The Thalidomide Tragedy – 25 Years Ago. *FDA Consumer*, v. 21, no. 1, February 1987. p. 17.

While these concerns prevented the drug's marketing in the United States,<sup>6</sup> the incident's publicity led to lengthy congressional hearings on the pharmaceutical industry, and eventual passage of the 1962 Kefauver-Harris Amendments.<sup>7</sup> These amendments not only tightened up existing safety testing requirements for drugs, they also required manufacturers to prove their product's effectiveness. Since then, federal law has required drug companies to prove that their products are both safe and effective before the FDA can approve them for marketing.

During the 1980s, Congress enacted several landmark drug laws that have had a lasting impact on the regulation of pharmaceuticals. While none of these legislative measures were aimed at changing the Act's basic safety and efficacy provisions, per se, in one way or another, they all left their mark on the drug approval process. In 1983, Congress passed the Orphan Drug Act (P.L. 97-414), which offers drug makers financial and marketing incentives to develop drugs for treating rare diseases. The following year it enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417).<sup>8</sup> Better known as the "Hatch-Waxman" law, it established a statutory mechanism to facilitate more rapid approval of generic drugs. At the same time, it gave drug companies added years of patent protection as compensation for marketing time lost during FDA review.<sup>9</sup> In 1988, these same patent benefits were given to producers of animal drugs under the Generic Animal Drug Patent Term Restoration Act (P.L. 100-670).

During the early 1990s, both consumer groups and the pharmaceutical industry became increasingly concerned about the length of time it was taking FDA to approve new drug products. In response, Congress looked for legislative ways it could speed up the drug review process without lowering approval standards, especially those that might compromise patient safety. With this goal in mind, it passed the 1992 Prescription Drug User Fee Act (PDUFA).<sup>10</sup> Under the user fee law, drug companies are assessed several different types of fees, including application fees, annual establishment fees, and product fees. The law stipulated that the extra revenues had to be used to hire additional reviewers and support staff, and upgrade FDA's information technology in order to reduce the time it took to review and approve drug marketing applications.

According to annual performance reports for PDUFA, approval times for new drug applications declined steadily after the law was enacted. Nonetheless, by the mid-1990s, the drug industry and other FDA reform advocates were contending that

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<sup>6</sup>In 1998, FDA approved thalidomide for treating leprosy.

<sup>7</sup>P.L. 87-781.

<sup>8</sup>For a comprehensive description of the Hatch/Waxman patent law see: CRS Report RL30765, *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984*, by Wendy H. Schacht and John R. Thomas.

<sup>9</sup>Drug companies usually file for patent protection as soon as a new compound is discovered. As such, the testing period and FDA review, often several years, counts as part of the total period of patent protection.

<sup>10</sup>P.L. 102-571.

the rate of drug approval could be increased even further if more sweeping statutory changes were adopted. After much debate and political compromise, Congress passed the 1997 Food and Drug Administration Modernization Act (FDAMA), the most comprehensive overhaul of the nation's food, drug, and medical devices laws in more than 30 years.<sup>11</sup> The reform measure not only reauthorized the 1992 user fee law, it also included numerous other provisions, many of them specifically tailored to limit or modify FDA's regulatory authority over foods, drugs, and medical devices.<sup>12</sup>

With the FDA Modernization Act, Congress adopted several measures it decided were needed to streamline clinical research and make it easier for drug companies to test and market new products. For example, in lieu of the full reports drug manufacturers were traditionally required to submit with marketing applications, Congress directed the FDA to issue guidance describing when companies would be allowed to submit abbreviated study reports instead. The agency was also instructed to set up a program to encourage further development of surrogate endpoints as predictors of a drug's therapeutic benefit.<sup>13</sup> In addition, Congress gave drug companies an additional 6 months of marketing exclusivity for testing the use of their drugs in pediatric patients. It also amended the FD&C Act so that the efficacy of a drug could, at FDA's discretion, be verified by just one, adequate and well-controlled study, along with confirmatory evidence.<sup>14</sup>

FDAMA also included provisions for the 'fast-track' approval of high priority drugs for treating life-threatening diseases, and expanded patients' rights to access investigational therapies.<sup>15</sup> However, while all of these measures, including the

<sup>11</sup>P.L. 105-115. For more detailed information on the FDA Modernization Act see: CRS Report 98-263, *Food and Drug Administration Modernization Act of 1997 – The Provisions*, by Richard Rowberg, B. Randall, Donna Porter, Bernice Reyes-Akinbileje and Donna Vogt, Science, Technology, and Medicine Division and Diane Duffy, American Law Division.

<sup>12</sup>Congress placed the regulation of medical devices under the Federal Food, Drug, and Cosmetic Act in 1976.

<sup>13</sup>The acceptance of 'surrogate endpoints' was established by FDA in its 1992 accelerated drug approval regulations. (See: *Federal Register*, v.57, no. 239, December 11, 1992. p. 58942.) Generally, surrogate endpoints are laboratory findings or physical signs that may not, in themselves, be a direct measurement of how a patient feels, functions, or survives, but nevertheless is considered likely to predict therapeutic benefit.

<sup>14</sup>P.L. 105-115, Section 115. The provision says that "if the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute "substantial evidence" ... for purposes of meeting the efficacy requirement. Prior to the FDA Modernization Act, FDA traditionally required at least two confirmatory studies to prove a drug's effectiveness.

<sup>15</sup>Even before FDAMA, FDA's review priorities always favored drugs for treating serious and life-threatening diseases. Moreover, the agency adopted rules in 1987 which made it easier for patients with serious medical complications to access experimental therapies (See: *Federal Register*, v. 52, no. 99, May 22, 1987.) In 1992, FDA ushered in its "parallel-track" policy that allows patients access to investigational drugs at the same time they are being used in

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requirement for pediatric testing,<sup>16</sup> were touted as needed legislative reforms, they were, for all practical purposes, little more than a codification of policies that FDA had already proposed or adopted through rulemaking.

## The Drug Approval Process

**How ‘Drug’ is Defined Under Federal Law.** The term “drug” has been officially defined in federal law for the better part of a century. The definition has been amended several times, however, mainly to extend its statutory reach. When Congress first outlawed the sale or transportation of adulterated or misbranded medicines under the Food and Drugs Act of 1906, it defined “drug” to mean:

all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals.<sup>17</sup>

Decades later, when Congress passed the Federal Food, Drug, and Cosmetic Act of 1938, it made a significant change in the way drugs would be characterized under the law.<sup>18</sup> With the 1938 amendments, the definition of drug was broadened so that the term would include not only substances that were intended to cure, mitigate, or prevent disease, but also any “articles” intended to affect the structure or function of the human body. Once Congress made these changes in the statute, almost any substance whose pharmacological action was intended to affect the structure or function of the human body in some way, could be deemed to be a drug by FDA for regulatory purposes.<sup>19</sup> The definition has remained the same ever since, and under current law, the term drug means:

articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary; ... and articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food)

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<sup>15</sup>(...continued)

clinical trials (See: *Federal Register*, v. 57, no. 73, April 15, 1992). Later that year the agency issued “accelerated approval” regulations for drugs to treat serious and life-threatening diseases (See: *Federal Register*, v. 57, no. 239, December 11, 1992).

<sup>16</sup>U.S. Dept. of Health and Human Services. Food and Drug Administration. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule. *Federal Register*, v. 63, no. 231, December 2, 1998. p. 66632.

<sup>17</sup>Pub. L. No. 384, Ch. 3915, Section 6.

<sup>18</sup>Pub. L. No. 717.

<sup>19</sup>Sometimes an item that is usually not considered a drug can become one if it is used in a way that affects the structure of the body of man. For example, common toothpaste, which would ordinarily be defined as a cosmetic since it can “cleanse, beautify, or promote attractiveness,” can also be regulated as a drug when the product contains fluoride and is labeled and promoted for reducing tooth decay.

intended to affect the structure or any function of the body of man or other animals; and articles intended for use as a component of any articles specified in [these] clauses.<sup>20</sup>

As a result of the 1938 law, all new drugs in the future would have to be tested for safety before they could be approved by the FDA for marketing. Along with the new premarket testing requirements, Congress added new language to the act defining how “new drugs” would be characterized from that point on. The statute also included the requirement that new drugs would have to become “generally recognized” as safe before they could be approved for marketing. The only exception was drugs previously marketed under the provisions of the 1906 Food and Drugs Act. These so-called “old” drugs were “grandfathered,” and considered exempt from the new safety testing requirements.<sup>21</sup> Under the 1938 act, a new drug was defined as:

Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof... or any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.<sup>22</sup>

When Congress expanded the definition of drug under the 1938 FD&C Act, it chose the word “articles” to describe the kinds of substances that if offered for the diagnosis, cure, or treatment of human disease, could potentially be covered by the statute. In other words, the term drug can be applied to virtually any item (i.e., article) that is marketed in interstate commerce, and is labeled or promoted for medicinal purposes. In the United States, the sale or marketing of pharmaceuticals without FDA approval is a violation of the FD&C Act.

The circumstances under which a substance might be regulated as a drug, has been debated ever since Congress defined the term. Generally speaking, products taken for their pharmacological effects, such as prescription or over-the-counter (OTC) medications, clearly meet the statutory definition of drug. For certain other products, however, even though they are also marketed as being therapeutic, the legal definition of drug may not apply. A good example would be certain food products, particularly dietary supplements. While dietary supplements are labeled and promoted for a number of suggested health benefits, they are not regulated as drugs, and, as

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<sup>20</sup>FD&C Act, Section 201(g)(1).

<sup>21</sup>Under the 1938 FD&C Act, Congress drew a legal distinction between “new drugs,” and so-called “old drugs.” Old drugs, those that entered medical use before 1938, were “grandfathered,” and considered exempt from retroactive safety testing.

<sup>22</sup>The FD&C Act (1938), Section 201(p).



such, need not undergo any safety and efficacy testing. Instead, Congress has deemed the products to be foods and has directed that they be regulated as such.<sup>23</sup>

**Drug Safety and Effectiveness.** All drugs – be they available by a doctor’s prescription, or sold more widely as OTC products – must be proven safe and effective before they can be approved in the United States. While prescription and nonprescription drugs are quite different, particularly in terms of their ingredients, labeling, and availability, many of the statutory requirements for marketing approval apply to both classes.<sup>24</sup> While the law requires drugs to be proven safe and effective before they can be approved by FDA, it does not specify just how safe and effective the drug must be. Moreover, even though safety and efficacy have to be confirmed through clinical testing, there is no guarantee that the drug will be equally safe and effective for all patients once it enters the mainstream of general medicine.

Even though the FD&C Act does not specify the same level of safety and efficacy for all pharmaceuticals, it does stipulate that FDA can approve a new drug for marketing only when its safety has been demonstrated by, “adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof.”<sup>25</sup> The agency is also prohibited from approving a new drug if, based on the clinical evidence submitted, there is, “a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.”<sup>26</sup> The key phrase “substantial evidence” is defined in the act to mean evidence:

... consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling ...<sup>27</sup>

When Congress passed the FDA Modernization Act of 1997, it avoided making wholesale changes that would undermine the basic statutory requirements for drug approval in the United States. Instead, it looked for other ways the testing and approval process could be sped up, while leaving the prerequisites for safety and efficacy alone. To this end, Congress reduced some of the paperwork involved in filing marketing applications, and clarified the number of clinical studies drug makers would need to do in order to gain FDA approval. The legislation also directed the

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<sup>23</sup>For more information on the regulation of dietary supplements see: CRS Report RL30887, *Dietary Supplements: Legislative and Regulatory Status*, by Donna V. Porter, March 14, 2001

<sup>24</sup>Hutt, Peter Barton and Richard A. Merrill. *Food and Drug Law, Cases and Materials*. 2<sup>nd</sup> Ed. Westbury, New York, The Foundation Press, Inc., 1991. 588 p.

<sup>25</sup>Section 505(d).

<sup>26</sup>Ibid.

<sup>27</sup>Ibid.

agency to issue guidance describing when drug companies would be allowed to file “abbreviated study reports” in lieu of the “full” reports, they were previously required to submit.<sup>28</sup> Moreover, as noted, unlike in the past where data from at least two, corroborative, well-controlled clinical studies were needed to confirm a drug’s effectiveness, under FDAMA, data from just one adequate and well-controlled clinical investigation, along with confirmatory evidence, can be sufficient to meet the law’s “substantial evidence” requirement.<sup>29</sup>

**Preclinical Research and Testing.** When a new chemical compound is discovered, the drug manufacturer or sponsor<sup>30</sup> carries out a series of preliminary experiments to find out how the substance works, and whether it may, one day, be safe enough for use in patients. The testing process typically begins in the company’s laboratory where scientists perform preliminary tests to see whether the drug has any affect on a disease or its symptoms in an appropriate animal model. At this early stage in testing, a drug is said to be undergoing preclinical evaluation. By federal law, all experimental drugs must be tested in animals before they can be given to patients in clinical trials.

During preclinical testing, the drug manufacturer’s main goal is to determine if the chemical compound is reasonably safe for initial use in humans, and whether it has enough pharmacological activity to justify further commercial development. To answer these questions, compounds with promising therapeutic potential are evaluated using a variety of testing methods that include not only live animals, but also *in vitro* (i.e., test tube) tests, tissue cell cultures, and computer driven data analysis systems. These studies can provide basic information about a drug’s toxicity, and in some instances, preliminary data about which dosage levels might prove to be unsafe in humans. The drug’s effects in animals are examined in detail, including the amount absorbed into the bloodstream, and the rate at which it is metabolized and eliminated by an intact, living organ system. In addition, these tests can provide valuable information about the new drug’s possible carcinogenic, mutagenic (causing genetic mutation), and teratogenic (abnormal fetal development) effects.

**The Investigational New Drug (IND) Application.** During preclinical research and testing, the majority of compounds being evaluated are, for a variety of reasons, found to be unworthy of further consideration. For those that merit further development, the results of the animal tests and lab work will be used to design a detailed protocol for eventual clinical trials in human subjects. When the decision is made to go forward with human clinical trials, the manufacturer must file an Investigational New Drug (IND) application with the FDA. The IND application is not a request for permission to market a new drug; instead, it is an exemption from

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<sup>28</sup>P.L. 105-115, Section 118.

<sup>29</sup>P.L. 105-115, Section 115. When FDA issued its guidance in August 1999, it said that “full study reports should [still] be submitted for all clinical and human pharmacology investigations that contribute to the evaluation of effectiveness for the proposed indication, or that otherwise support information included in labeling.”

<sup>30</sup>The term “sponsor” usually means the person or agency who assumes responsibility for an investigation of a new drug.

the statutory prohibition against shipping experimental drugs in interstate commerce without FDA approval. Drugs with approved INDs, however, can be legally shipped and administered to patients enrolled in clinical investigations.

When a drug manufacturer or other sponsor files an IND, they must submit all information and data from preclinical studies, an explanation of the investigational drug's intended medical use, and a full description of the clinical trial protocols designed to document the drug's safety and effectiveness. The IND must specify how many patients will be involved in the clinical trials, how the drug will be administered (i.e., oral versus injectable), and the dosage level that will be given. Information about the drug's chemical composition and manufacturing process is also required. An IND must also include the names and qualifications of the clinical investigators involved, and where the studies will be conducted. The FDA has 30 days to review an IND, and if it has no objection to the protocol's design, the sponsor can begin clinical testing. In situations where FDA has concerns about an application, it can place the IND on "clinical hold."<sup>31</sup> Once an IND has been placed on clinical hold, the investigation can proceed only with the agency's approval.

FDA regulations acknowledge several types of INDs, depending on the needs of the drug sponsor, or the kind of clinical investigation involved. Commercial INDs are those typically filed by a drug manufacturer so they can begin clinical testing. In 1987, however, the agency issued regulations establishing the so-called "treatment IND." Also known as "compassionate INDs," these exemptions are granted so that patients with serious or life-threatening diseases or conditions can gain access to promising experimental drugs for treatment purposes without being part of the formal clinical trial. To be granted treatment IND status, the experimental drug must be under active clinical investigation, cannot be promoted or sold during the clinical trials, and the manufacturer must be actively pursuing marketing approval. Moreover, in situations where treatment INDs are involved, the drug company must agree to make the drug available, and the patient's doctor must be willing to administer the drug and then monitor and record its effects.

Drug manufacturers or sponsors usually arrange with physicians, hospitals, or clinical centers to carry out and/or direct the clinical investigations. By FDA regulation, every investigation involving human test subjects must be overseen by an Institutional Review Board (IRB).<sup>32</sup> IRBs are required to have at least five members, with varying backgrounds (e.g., medical ethicist, clergy, and physicians), who have the experience and expertise to evaluate the ethical aspects of the proposed study and protect the rights and welfare of the human subjects involved. Review boards have the authority to approve, modify, or disapprove research protocols. Before a clinical trial can begin, IRB members must also ensure that the informed consent obtained

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<sup>31</sup>21 C.F.R. 312.42. Imposing and lifting clinical holds.

<sup>32</sup>21 C.F.R. Part 56, Institutional Review Boards. Also, under 21 C.F.R. 312.66, clinical investigators must assure that an IRB that complies with the requirements of Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study.

from the study subjects complies with the requirements in the Protection of Human Subjects regulations.<sup>33</sup>

**Clinical Trials.** When the FDA has reviewed an IND's animal test data and concluded that the investigational drug is safe enough to be tested in humans, clinical (human) studies can begin. These studies, or clinical trials, are usually carried out in three phases. Phase I studies focus on assessing the drug's safety in a group of healthy volunteers, usually at very small doses in fewer than 100 patients. These preliminary tests are intended to help pharmaceutical companies find out whether small doses of the drug cause any immediate safety problems that could make continuation of the trial impossible. The information gathered from these small trials will make it easier for investigators to determine whether the drug's dosage needs to be adjusted before it is given to a larger number of study participants in the testing phases that lie ahead. At this juncture, if no serious or unexpected complications have emerged, the clinical testing moves on to Phase II.

In general, Phase II trials are randomized, well-controlled, double-blind clinical investigations. While controlled studies are important to verify further a drug's safety, their main purpose is to find out whether the drug is effective or not. Typically, the studies are designed, or set up, so that a group of patients who are given the active drug – the “treatment” group – is compared to a “control” group of patients who share similarities in age, sex, and disease characteristics, but are given a placebo, or dummy pill instead. Investigators have several different kinds of controls they can use, depending on the study's objective, knowledge of the disease being treated, and whether there are viable, alternative therapies available. Further, these trials are also “blinded,” meaning that neither the investigators nor the patients know which group of patients is receiving the active drug or the placebo. Phase II studies typically involve several hundred patients.

Phase III clinical trials can involve both controlled and uncontrolled studies and may include as many as several thousand patients. These trials produce additional information about safety and effectiveness, help define the drug's overall benefit-to-risk ratio, and determine how its official labeling will be worded. The larger studies are intended to provide more information on the drug's side effects, whether it interacts with foods and/or other medications, and whether certain patient populations should avoid its use altogether.

Quite often, investigational drugs seem to be relatively safe and effective in the early stages of testing. However, when the drug is administered to a much larger patient population, particularly during later, more tightly controlled trials, only then will the unanticipated, potentially serious side effect begin to show up. In a similar context, compounds that looked as though they might be very effective based on preliminary data, are sometimes shown to offer patients little or no therapeutic benefit in later controlled studies. Also, drug makers know that once a drug's clinical trials have been completed, and a marketing application has been filed, the FDA will examine their test results very carefully. Whether the drug will be approved ultimately

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<sup>33</sup>45 C.F.R. 46.

rests with the agency's interpretation of the safety and efficacy data generated during the clinical trials.

**The New Drug Application (NDA): FDA Review.** If clinical studies confirm that a new drug is relatively safe and effective, and will not pose unreasonable risks to patients, the manufacturer files a New Drug Application (NDA), the actual request to manufacture and sell the drug in the United States. The NDA must include all data from animal and laboratory testing, comprehensive information about the drug's chemistry and pharmacology, and the complete results of all clinical investigations.<sup>34</sup> Samples of the finished product and copies of the drug's proposed labeling must also be included. In addition, the application must include information about the facilities where the drug will be produced, and provide assurances that the finished product will be made in accordance with current good manufacturing practices (GMPs).<sup>35</sup> When an NDA is reviewed, agency statisticians and epidemiologists closely examine the drug's safety and efficacy data. At the same time, samples of the drug undergo laboratory analysis, while other officials check to make sure that the product's official labeling is comprehensive, scientifically accurate, and not misleading. The entire review process can take months to several years to complete, depending on the size and complexity of the application.

By law, FDA does not require drug companies to prove that a new drug will be 100 % safe and effective for all patients before it can be approved for medical use. For pharmaceutical products, such absolute certainty is infeasible, if not impossible to obtain. There is no such thing as a completely risk free drug; and all produce unwanted side effects in a small percentage of patients. Instead, when the FDA examines a drug's safety and efficacy profile, it focuses on the quality and totality of the clinical trial data. Once the agency analyzes the data, it decides from a statistical standpoint, whether the product's "benefit-to-risk" ratio is sufficient to support its approval. In general, FDA tries to apply this "benefit-to-risk" policy the same way for all marketing applications. From time to time, however, the agency will approve a drug with a higher risk profile, particularly if the drug may benefit patients with a serious or life-threatening disease, and there is no other alternative therapy available.

When an NDA is reviewed, FDA officials will often meet simultaneously with the sponsor to discuss possible deficiencies the application may have. For example, if the agency has serious concerns about the sufficiency of the drug's safety and efficacy data, it may insist the company do additional studies or data analysis. Only when these studies are done, and the agency is satisfied with the additional data, will the application be considered for approval. Questions that involve minor discrepancies must be resolved to FDA's satisfaction before final approval is given. Under the FD&C Act, FDA has 180 days to either approve or disapprove an NDA.

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<sup>34</sup>The information contained in an NDA used to fill numerous, mostly paper, volumes. In today's computer environment, the same filing can be done in electronic format.

<sup>35</sup>Section 501(a)(2)(B) of the FD&C Act declares that a drug must be deemed adulterated if the methods, facilities, and controls used for its manufacture, processing, packaging, are not in conformity with current good manufacturing practices (GMPs). GMP regulations for drugs are codified at 21 C.F.R. 210 and 211.

Reviews not completed within that time frame are usually extended by mutual consent, particularly if the agency believes additional safety studies are needed.

The FDA can refuse to approve a drug's marketing application for any number of reasons, most of which relate to serious deficiencies in the sponsor's NDA. By law, approval can be denied if the application does not include adequate tests, done by conventional methods, to prove that the product can be safely used for the medical conditions described or suggested in its labeling. In addition, the application could be denied if the clinical data were insufficient, in FDA's judgement, to show that the drug was effective. Where safety and effectiveness are not an issue, final approval could be delayed if the agency has concerns that the facilities and controls used for production and packaging are inadequate to preserve the finished product's pharmacological integrity (i.e., its identity, strength, quality, and purity).

When the review reaches its final stage, FDA will notify the manufacturer that the drug is either approved for marketing, would be approved if some last-minute changes are made, or cannot be approved because the test data do not support the drug's safety and efficacy. At this point in the review process, refusing to approve an application is fairly unusual. Should this happen, however, the drug's sponsor can choose to withdraw the application or request a hearing.<sup>36</sup> If a hearing is granted, the sponsor bears the burden of convincing the agency to reconsider its decision to deny approval.

**Generic Drug Approval.** The review and approval of generic drugs is quite similar to that of brand name products.<sup>37</sup> According to the FDA, generic drugs are identical to brand name pharmaceuticals in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.<sup>38</sup> Most brand name drugs are developed and marketed with the benefit of patent protection. Drug patents give innovator pharmaceutical companies a period of marketing exclusivity, which allows them to recoup their research and development costs. When a drug's patent(s) or marketing exclusivity expires, however, other manufacturers are free to produce the drug in its generic form. Under the Drug Price Competition and Patent Term Restoration Act of 1984, manufacturers of generic drugs are allowed to submit abbreviated new drug applications (ANDAs) to market their products.<sup>39</sup>

An ANDA is considered "abbreviated" because the sponsor is not required to reproduce the clinical studies that were done for the original, brand name product. Instead, generic drug manufacturers must demonstrate that their product is the same as, and bioequivalent to, a previously approved brand name product.<sup>40</sup> Generally,

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<sup>36</sup>21 C.F.R. 314.200. Hearing Procedures for New Drugs.

<sup>37</sup>*From Test Tube to Patient: Improving Health Through Human Drugs*. An FDA Center for Drug Evaluation and Research, Special Report. September 1999. p. 62.

<sup>38</sup>See: FDA, Office of Generic Drugs, [<http://www.fda.gov/cder/ogd/index.htm>].

<sup>39</sup>See footnote 8.

<sup>40</sup>21 C.F.R. 320.1(e). FDA regulations state that drug bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety  
(continued...)

bioequivalence is established by producing scientific data verifying that the generic drug will deliver into the bloodstream of health test volunteers, the same amount of active ingredient, in the same amount of time, as the innovator's product. In addition to bioequivalence, generic drug makers must also provide assurance that their products meet all U.S. Pharmacopoeial standards, and are properly labeled. Finally, the facilities where the finished product will be made must undergo FDA inspection, and the manufacturer must certify that the finished product will be made in accordance with good manufacturing practices and procedures.

All approved drug products, both brand name and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, the so-called "Orange Book."<sup>41</sup> Named for the color of its cover, the *Orange Book* is a cumulative agency publication that lists drug products that are bioequivalent, including new drugs, generic drugs, and some antibiotics. It also includes information about approved nonprescription drugs, drug patent listings, and time periods for market exclusivity.<sup>42</sup> Using a coded lettering system, the *Orange Book* identifies the approved drugs the agency considers to be therapeutically equivalent – those designated by the "A" codes, and those it believes have documented bioequivalence problems – indicated by the "B" codes. By making this sort of information available, including on-line, the *Orange Book* gives physicians, dispensing pharmacists, and patients an unbiased source to help them decide when therapeutically equivalent generic drugs can be substituted for brand name products.

## Post-Marketing Surveillance

As a health protection agency, the FDA is responsible for monitoring the safety of pharmaceutical products once they are approved for marketing in the United States. To do this, the agency relies on several post-marketing surveillance systems, designed to watch for safety problems that sometimes arise, especially in newly approved products that are being prescribed for the first time. Under FDA's adverse drug reporting system, the legal obligation to report side effects or adverse experiences is different for pharmaceutical companies than it is for health professionals and consumers. By regulation, pharmaceutical companies must report all serious and unexpected adverse drug experiences they become aware of, no matter

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<sup>40</sup>(...continued)

in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

<sup>41</sup>See FDA's: *Approved Drug Products with Therapeutic Equivalence Evaluations*. [<http://www.fda.gov/cder/ob/default.htm>].

<sup>42</sup>Market "exclusivity" refers to a period of time, often several months or years, that pharmaceutical companies are given to market a drug, during which the FDA is not allowed to approve the same product made by another manufacturer. In the 1980s, Congress granted drug makers periods of market exclusivity under the Orphan Drug Act and the Drug Price Competition and Patent Term Restoration Act. More recently, under the 1997 FDA Modernization Act, Congress gave drug companies 6 additional months of exclusivity for determining the safe use of drugs in pediatric populations.

the source, to the FDA within 15 days.<sup>43</sup> However, even though doctors, health care professionals, and consumers are encouraged to report adverse drug experiences as well, their participation in the post-marketing surveillance process is strictly voluntary.

Post-approval monitoring of drug safety is essential for several reasons, not the least of which is watching for adverse effects that often do not show up until the drug is on the market. In early clinical investigations, experimental drugs are usually tested on a relatively small number of study participants, usually a few hundred, to several thousand patients. Under these limited, tightly controlled conditions, a side effect that occurs in only 1 out of 10,000, or possibly 1 out of 100,000 patients, may not have materialized at that point in testing. However, once the new drug reaches the market, and is prescribed for a much larger population of patients, perhaps numbering hundreds of thousands, if not millions, the probability of adverse effects increases substantially. A post-market reporting system helps FDA officials determine whether adverse effects in such large user populations are serious enough to warrant some kind of regulatory action.

In 1993, the FDA updated its post-marketing surveillance capabilities, and established a more global monitoring system under the name MedWatch.<sup>44</sup> According to the agency, the MedWatch program was designed to make it easier for health professionals (i.e., doctors, nurses, pharmacists, etc.), and the general public, to voluntarily report side effects and other health problems related to the use of prescription drugs, biologics,<sup>45</sup> and medical devices. Adverse effects associated with the use of over-the-counter drugs, dietary supplements, infant formulas, and medical foods can also be reported using the system. Adverse reactions attributable to vaccines, however, are reported to their own surveillance program, the Vaccine Adverse Event Reporting System (VAERS), rather than to MedWatch. When adverse reactions are reported to the FDA, they are entered into MedWatch's post-marketing surveillance database for further evaluation. At this stage, the collected data are analyzed to find out if there is a causal relationship between the use of a drug and the reported adverse reactions. When this determination is made, the information is forwarded to the appropriate center where FDA officials decide whether some kind of public notification is needed.

Recently, the MedWatch surveillance system has helped FDA decide whether a number of pharmaceutical products, suspected of causing serious side effects in some patients, should be allowed to remain on the market. In 1998, after post-marketing reports linked the anti-inflammatory drug Duract (bromfenac) with severe liver problems in some patients, the product was voluntarily withdrawn from the market by its manufacturer Wyeth-Ayerst Laboratories.<sup>46</sup> That same year, the drug Posicor

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<sup>43</sup>21 C.F.R. 314.80

<sup>44</sup>MedWatch: The FDA Medical Products Reporting & Safety Information Program. [<http://www.fda.gov/medwatch/>].

<sup>45</sup>Biologics are products derived from living sources such as humans, animals, and microorganisms.

<sup>46</sup>Wyeth-Ayerst Laboratories Announces the Withdrawal of Duract From the Market. *FDA* (continued...)



(mibefradil), an anti-hypertensive, was voluntarily withdrawn by its maker Roche Laboratories, after new reports linked it with potentially harmful interactions with other drugs.<sup>47</sup>

In February 2000, the drug Lotronex (alosetron HCL), a prescription drug manufactured by Glaxo Wellcome, received FDA approval for treating Irritable Bowel Syndrome (IBS) in women. Shortly thereafter, FDA became concerned when early post-marketing reports linked Lotronex to cases of intestinal damage resulting from ischemic colitis (reduced blood flow to the intestine) and severely obstructed or ruptured bowels.<sup>48</sup> To address these concerns, FDA convened its Gastrointestinal Drugs Advisory Committee in June to discuss various risk management options. Among the factors discussed was the fact that many IBS patients taking Lotronex did not experience adverse effects, and wanted to continue their treatment. The advisory committee recommended that immediate steps be taken to inform both physicians and patients of the adverse effects associated with the drug's use.

In August, Glaxo Wellcome responded, updating Lotronex's professional labeling, and distributing medication guides warning patients about the drug's potential health risks. In addition, the company mailed letters informing doctors and pharmacists of the new safety information. In November, after receiving more reports of serious adverse reactions, including reports of several deaths in patients taking Lotronex, the FDA offered Glaxo Wellcome the option of withdrawing the drug, or agreeing to restricted distribution under the agency's new risk management program. According to the agency, the risk management program for Lotronex had to include: safer use of the drug in appropriately informed patients; continued access to Lotronex by severely affected patients under closely monitored conditions; and continued clinical studies of the benefits and risks, and safe use of the drug.<sup>49</sup> After further discussions, Glaxo Wellcome decided that FDA's risk management offer wasn't in their best interest, and, on November 28, 2000 opted to withdraw Lotronex from the market.

At this point, the availability of Lotronex in the immediate future is uncertain. Despite the withdrawal, patient demand for the drug still remains high. In January 2001, the manufacturer (now GlaxoSmithKline (GSK) after a merger) and FDA officials were reportedly having discussions about the possibility of bringing Lotronex

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<sup>46</sup>(...continued)

*Talk Paper*, Food and Drug Administration. June 22, 1998.  
[<http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html>].

<sup>47</sup>Roche Laboratories Announces Withdrawal of Posicor From the Market. *FDA Talk Paper*, Food and Drug Administration.  
[<http://www.fda.gov/bbs/topics/ANSWERS/ANS00876.html>].

<sup>48</sup>Glaxo Wellcome Decides to Withdraw Lotronex From the Market. *FDA Talk Paper*, Food and Drug Administration. November 28, 2000.  
[<http://www.fda.gov/bbs/topics/ANSWERS/ANS01058.htm>].

<sup>49</sup>Glaxo Lotronex Withdrawal Follows Failed Risk Management Negotiations. *The Pink Sheet*, v. 62, no. 49, December 4, 2000. p. 3.

back, albeit with specific restrictions.<sup>50</sup> These discussions are apparently continuing as GSK and the agency try to figure how to identify risk factors for Lotronex adverse events, and the best way to incorporate those factors into a risk management plan for irritable bowel syndrome therapy. However, some have expressed strong concerns about Lotronex being reintroduced, even under a limited access plan. In a April 18 letter to FDA, the consumer advocacy group *Public Citizen* said that the drug should only be available to patients who have used it and have not experienced adverse effects.<sup>51</sup>

As these examples illustrate, when reports indicate that a drug product may be causing serious side effects in patients, FDA has several objectives: analyze the magnitude of the health risks involved; find out if the drug in question is actually responsible, and decide whether these factors, taken together, justify some sort of remedial action. Depending on the severity of the reactions, and how great a health threat they pose, the agency has several regulatory options to choose from. For that rare occasion where the side effects associated with a drug are so serious that they pose an “imminent hazard” to public health, Congress authorized the Secretary of Health and Human Services to suspend the marketing of a drug immediately.<sup>52</sup> To do this, however, the Secretary must be able to show that the drug is so dangerous that without its immediate suspension, these will likely be further injury and harm to public health.<sup>53</sup> Since these criteria are very hard to meet, the Secretary has invoked imminent hazard clause in only a handful of cases.

When a drug’s adverse effects aren’t serious enough to justify complete market withdrawal, the FDA relies on other means to help patients understand the risks involved. A fast and common method is to issue a public announcement or general warning through the media and its own Website. If necessary, the agency sends out “Dear Health Professional” letters, which passes the latest information about adverse effects along to doctors and pharmacists. This same kind of information is also disseminated by the manufacturer through similar channels. As this is being done, the FDA will contact the manufacturer to discuss changes in the drug’s professional labeling that will reflect the new safety concerns. Moreover, when the product’s labeling is updated, the manufacturer may be required to use a so-called “boxed-warning,” especially if the FDA decides that the new warning information has to be displayed more conspicuously.

After a time, if these efforts don’t seem to be protecting the health and safety of patients, and reports of serious side effects continue to grow, FDA can offer the manufacturer one of two things. As in the Lotronex situation above, it can request that the drug be available only through a limited distribution program, or it can urge the manufacturer to consider withdrawing the drug from the market.

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<sup>50</sup>Grady, Denise. FDA Pulls a Drug, and Patients Despair. *The New York Times*, Health & Fitness, Section F, January 30, 2001, p. 1.

<sup>51</sup>Lotronex Risk Factor Identification Is Prerequisite To Return, FDA Says. *The Pink Sheet*, v. 63, no. 17, April 23, 2001. p. 10.

<sup>52</sup>Section 505(e), FD&C Act.

<sup>53</sup>See: 21 C.F.R. 2.5, Imminent Hazard to the Public Health.

## Conclusion

Ever since Congress first outlawed the sale of adulterated or misbranded products in the early 1900s, the statutes and rules that govern the drug approval process today have grown numerous and complex. Nevertheless, by the close of the twentieth century, these very drug laws had raised testing standards, assured veracity in labeling, and provided U.S. consumers with an unparalleled supply of safe and effective medicines.

Today, the United States has perhaps the toughest drug approval standards in the world. Before new drugs can be sold, pharmaceutical manufacturers are required by law to produce large amounts of clinical data demonstrating that products are both safe and effective. In addition, safety and efficacy have to be proven through rigorous, well-controlled clinical trials, investigations that are scientifically demanding and expensive to conduct. Although the FD&C Act requires that all drugs be proven safe and effective, it doesn't specify just how safe and effective they have to be. For this reason, the FDA has a lot of discretion in deciding whether a drug's clinical data are sufficient to meet the statutory requirements for marketing approval.

The speed with which FDA reviews and approves new pharmaceuticals is measured more closely than any of its regulatory functions. As such, the agency faces ongoing pressure from Congress, the U.S. pharmaceutical industry, and patient advocacy groups to approve new drugs as quickly as possible. In the 1990s, Congress passed several bills aimed specifically at speeding up the approval process. In 1992, with drug industry cooperation, it passed the first ever drug user fee law, legislation which many feel has contributed greatly to faster application reviews. Subsequently, again with strong industry support, it enacted the FDA Modernization Act of 1997. With this latter FDA reform measure, Congress extended the original user fee law for another 5 years, revised and streamlined certain drug testing requirements, and demanded more timely approval of pharmaceutical products.

Many of the major advances in the quality of U.S. health care over the past 50 years were brought about with the help of pharmaceutical technology. Diseases, which lacked reliable treatment just decades ago, can today be cured, or at least managed through the use of safe and effective drugs and vaccines. In recent decades, as public demand for safer, more effective "high-tech" medicines has increased, so too have the costs of research and development, and the price of drugs as well. As the nation's health care system comes to rely more on the use of pharmaceuticals each year, the laws and policies that affect the drug approval process become more important.