How Are Drugs Approved?

Part 1: The Evolution of the Food and Drug Administration

ABSTRACT

The discovery, development, and marketing of drugs for clinical use is a process that is complex, arduous, expensive, highly regulated, often criticized, and sometimes controversial. In the United States, the Food and Drug Administration (FDA) is the governmental agency responsible for regulating the development and marketing of drugs, medical devices, biologics, foods, cosmetics, radiation-emitting electronic devices, and veterinary products, with the objective of ensuring their safety and efficacy. As part of a broad overview of the drug development process, this article will describe the historical evolution of the FDA. This will provide background for two subsequent articles in this series, which will describe the ethical foundations of clinical research and the stages of drug development.

The discovery, development, and marketing of drugs for clinical use is a process that is complex, arduous, expensive, highly regulated, often criticized, and sometimes controversial (Hollander, 2006; Miller, 2005; Rivas-Vazquez, 2002; Wood, 2006). In the United States, the Food and Drug Administration (FDA) (n.d.) is the governmental agency responsible for regulating the

ROBERT H. HOWLAND, MD

development and marketing of drugs, medical devices, biologics, foods, cosmetics, radiation-emitting electronic devices, and veterinary products, with the objective of ensuring their safety and efficacy. With a broad overview of the drug development process, nurses will better understand the issues involved in bringing a drug to market. The first article of this three-part series will describe the historical evolution of the FDA. This will provide background for the two subsequent articles in this series, which will describe the ethical foundations of clinical research and the stages of drug development.

THE FDA FROM 1906-1997

The federal government's oversight of the drug industry began with the passage of the original Pure Food and Drugs Act of 1906 (Lipsky & Sharp, 2001). This legislation required that drugs meet official standards of strength and purity, defined the terms *adulterated* and *misbranded*, and prohibited interstate commerce in adulterated and misbranded foods and drugs. The Meat Inspection Act was also passed at the same time. These two laws were enacted following shocking disclosures of unsanitary conditions in meat-packing plants, the use of poisonous preservatives and dyes in foods, and cure-all claims for worthless and dangerous patent medicines.

Drug Safety

Despite the existence of this legislation, a marketed patent medicine, elixir sulfanilamide, killed 107 individuals (including many children) in 1937 (Steinbrook, 2002). The compound contained the poisonous solvent diethylene glycol. Chemists used this solvent to make a liquid formulation ("elixir") of the antibacterial agent sulfanilamide, which would make it easier for children to take. Although chemists knew of the solvent's toxicity at the time, the manufacturer who used the chemical process to produce the elixir for marketing did not know about the toxicity.

Because the 1906 Act did not require manufacturers to demonstrate the safety of a drug, the Federal Food, Drug, and Cosmetic Act was enacted in 1938 (Swann, 1998). The main provision of this Act was the requirement that new drugs must be shown to be safe by the manufacturer (rather than by the FDA) before marketing the drug. This started an entirely new system of drug regulation. In addition, this Act eliminated a previous requirement to prove intent to defraud regarding the ingredients or labeling of a drug. Hence, a manufacturer would become liable for any statements about the ingredients, identity, or therapeutic claims of a drug that are false or misleading, regardless of whether there was intent to defraud.

The Act also established the need to set safe tolerances for unavoidable poisonous substances (i.e., safe exposure levels to chemicals used commercially or industrially). Other provisions of the Act were to extend oversight control to cosmetics and therapeutic devices; to authorize standards of identity, quality, and fill-of-container for foods; to authorize factory inspections; and to add the remedy of court injunctions to the previous penalties of seizures and prosecutions for violations.

In response to the 1938 Act, the FDA began regulating the advertising, labeling, and dispensing of drugs (Lipsky & Sharp, 2001). In particular, this included a new policy that certain drugs deemed potentially dangerous be administered under the direction of a qualified expert, which started the requirement that such drugs be available only by prescription. Until 1951, the decision to label a drug for prescription-only use was largely at the discretion of the manufacturer. However, the Durham-Humphrey Amendment (1951) specifically defined the kinds of drugs that cannot be used safely without medical supervision and thereby restricted their sale to prescription by a licensed practitioner.

In 1961, a new drug for sleep (thalidomide), used extensively in western Europe, was found to have caused birth defects in thousands of babies. Although the FDA did not approve the drug for use in the United States, publicity about this tragedy led to calls for stronger drug regulation in the United States. Consequently, the Kefauver-Harris Amendments (1962) were passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to the FDA the effectiveness of their products before marketing them. With this landmark legislation, the FDA received closer control over investigational drug studies; FDA inspectors were granted access to additional manufacturer records; and manufacturers were required to demonstrate the efficacy of products approved prior to 1962.

Drug Abuse and Nonprescription Drugs

Drug Abuse Control Amendments (1965) were enacted to handle problems caused by abuse of depressant, stimulant, and hallucinogenic agents. The Comprehensive Drug Abuse Prevention and Control Act (1970) replaced previous laws and categorized drugs on the basis of abuse and addiction potential, in addition to their therapeutic value. In 1966, the

FDA contracted with the National Academy of Sciences/National Research Council to evaluate the effectiveness of 4,000 drugs approved based on safety alone between 1938 and 1962. The FDA formed the Drug Efficacy Study Implementation program in 1968 to incorporate their recommendations. The Over-the-Counter Drug Review was initiated in 1972 to enhance the safety, effectiveness, and appropriate labeling of nonprescription drugs. The Vitamins and Minerals Amendments (1976) prohibited the FDA from establishing standards limiting potency of vitamins and minerals in food supplements or regulating them as drugs on the sole basis of potency.

Much later, the Dietary Supplement Health and Education Act (1994) established a formal regulatory framework for dietary supplements, including specific labeling requirements and good manufacturing practice regulations. This Act defined *dietary supplements* and *dietary ingredients*, classified them as foods rather than as drugs, and established a commission to recommend how to regulate claims. The FDA published a rule on dietary supplements in 2000, further defining the kind of statement that can be labeled regarding the effect of supplements on the human body's structure or functioning (FDA, 2000).

Investigational Drugs

The Orphan Drug Act (1983) enabled the FDA to promote research and marketing of drugs for treating rare diseases. In 1987, partly in response to the AIDS epidemic, the FDA revised investigational drug regulations to expand access to experimental drugs for patients with serious diseases that have no alternative therapies (Lipsky & Sharp, 2001). The intent was to accelerate approval for high-priority medications. Before 1987, drugs were approved based on their effect on the illness or on survival. With this policy change, the FDA could evaluate drugs on the basis of surrogate endpoints (i.e., the effect of a drug on a physiological process or biochemical marker associated with the disease) and could approve promising drugs without necessarily completing full clinical trials. These regulations were further modified in 1991 to accelerate reviews of drugs for life-threatening diseases.

Generic Drugs

The Drug Price Competition and Patent Term Restoration Act (1984) expedited the availability of generic drugs (Frank, 2007). This important Act permitted the FDA to approve generic versions of brand-name drugs without repeating the research conducted to prove them safe and effective. It also allowed the manufacturers of brand-name drugs to apply for up to 5 years of additional patent protection for their products to compensate for time lost while their products were going through the FDA's approval process. Prior to 1984, generic-drug makers were obligated to conduct the same efficacy and safety tests required of the original brand-name drug manufacturer (Welage, Kirking, Ascione, & Gaither, 2001).

In accordance with this Act, generic-drug manufacturers were required only to establish bioequivalence to the active ingredients of the original drug and to demonstrate adherence to FDA-approved manufacturing processes. Bioeqivalence signifies that similar serum concentrations are achieved when the generic medication is administered in the same manner as the brand formulation. Regulatory agencies typically require the bioequivalence of generic drugs be within the rather broad range of 80% to 125% of the brand medication (Blier, 2007).

Drug Development

The Prescription Drug User Fee Act (1992) required for the first time drug manufacturers to pay fees for product applications and that the FDA use these funds to hire more reviewers to assess applications, with the intent of expediting the review process. MedWatch, a consolidation of several adverse reaction reporting systems, was first launched in 1993 for health professionals to voluntarily report to the FDA problems associated with medical products. The FDA issued new guidelines in 1993 for improved assessments of medication effects according to gender, revising a policy from 1977 that excluded women of childbearing potential from early drug development studies. Companies were encouraged to include male and female patients in their drug development trials and analyze any gender-specific phenomena.

FDA MODERNIZATION ACT OF 1997

The Food and Drug Administration Modernization Act (FDAMA) of 1997 led to the most extensive changes since 1938 of many FDA practices and regulations (FDA, 2002). One of the most important mandates of the FDAMA was developing a publicly accessible database on clinical trials. As a result, the Web site http://www.ClinicalTrials.gov was created in 2000 to provide useful information about drug studies regulated by the FDA, although initially, the authorization only applied to experimental drugs for serious or life-threatening diseases.

Another significant change as a result of the FDAMA was the

establishment of specific standards and guidelines for providing clinical evidence of effectiveness for drugs and biological products. For example, the law codified the FDA's practice of allowing, in certain circumstances, one clinical investigation as the basis for product approval, but preserved the general rule that two adequate and well-controlled studies are needed to prove the product's safety and effectiveness. These last provisions, in particular, were most relevant for the specific development of good guidance practices for FDA decision making.

The FDAMA also abolished the long-standing prohibition on manufacturers' dissemination of information about unapproved uses of drugs and medical devices. This allowed companies to disseminate peer-reviewed journal articles about off-label indications of their products, provided the companies committed themselves to filing supplemental applications based on appropriate research to establish the safety and effectiveness of the unapproved use. This also allowed drug companies to provide economic information about their products to formulary committees, managed care organizations, and other large-scale buyers of health care products. This was intended to provide such entities with dependable facts about the economic consequences of their procurement decisions; however, the FDAMA did not permit the dissemination of economic information to individual medical practitioners that could affect prescribing choices. The reason for this distinction was to prohibit potential financial influences on individual medical decision making.

The FDAMA increased patient access to experimental drugs and accelerated the review of important new medications. The FDAMA created a special exemption to ensure continued availability of compounded drug products prepared by pharmacists to provide patients with individualized therapies not available commercially. In 1999, a final rule based on the FDAMA mandated that all over-the-counter drug labels must contain data in a standardized format. These drug facts were designed to provide patients with easy-to-find information, analogous to the nutrition facts label for foods.

To fulfill another important requirement of the FDAMA, the FDA promulgated the Pediatric Rule (1998). This regulation required manufacturers of selected new and existing drugs to conduct studies to assess their safety and efficacy in children. In exchange for carrying out these studies, the FDA would extend the market exclusivity of a drug by 6 months. The Best Pharmaceuticals for Children Act (2002) further improved the safety and efficacy of patent and off-patent medicines for children and continued the exclusivity provisions for pediatric drugs mandated by the FDAMA. The 2002 Act clarified aspects of the exclusivity period and amended procedures for generic drug approval in cases when pediatric guidelines are added to the labeling. The FDA was given clear authority under the Pediatric Research Equity Act (2003) to require that companies conduct clinical research into pediatric applications for new drugs.

FDA AMENDMENTS ACT OF 2007

Most recently, Congress enacted the Food and Drug Administration Amendments Act (FDAAA) of 2007 (FDA, 2007). The FDAAA has further changed and expanded many of the FDA's responsibilities and powers, with a particular emphasis on drug safety and surveillance. The FDAAA authorizes that drug manufacturers pay fees for product applications and that the FDA use these funds for the initial review process, for the monitoring of drugs after they are marketed, and for a new program to support FDA review of television drug advertisements directed at consumers. New guidelines regulating conflicts of interest of FDA advisory board members were also established.

The FDAAA also mandates an expansion of the publicly accessible clinical trials database, http://www.ClinicalTrials.gov, to require drug companies and other organizations to make public their studies of approved drugs (not just experimental) for all kinds of disorders (not just serious or life threatening). In addition to clinical trial registry information, this database will also be required to include basic trial results for approved drugs (Drazen, Morrissey, & Curfman, 2007). It is conceivable that the database could be expanded to include adverse event information about approved and unapproved drugs, as well as trial registries for unapproved products.

Another major provision of the FDAAA is to create a private, independent, nonprofit foundation to advance the mission of the FDA to modernize medical, veterinary, food, food ingredient, and cosmetic product development; accelerate innovation; and enhance product safety. The foundation will identify unmet scientific needs in the development, manufacturing, and evaluation of the safety and effectiveness of FDA-regulated products, including postmarket evaluation, and establish scientific projects and programs to address those needs. It will help accomplish the scientific work the FDA needs to support its regulatory mission.

Finally, a variety of provisions covered in a section of the FDAAA titled "Enhanced Authorities Regarding Postmarket Safety of Drugs" is intended to fundamentally change the FDA's mission to include the oversight of a drug's safety after its approval (Schultz, 2007). Although the FDA can request that companies include warnings and other critical information on a drug's label after drug approval, it has never had the power to order such changes. Under the FDAAA, after a 30-day period of negotiation, the FDA can order a labeling change. When the risks associated with a drug justify close control of its use, the FDA will have the authority to restrict its distribution to physicians in particular specialties or to particular settings. The FDA also has new authority to order manufacturers to conduct postmarketing studies of approved drugs to identify and assess serious drug risks or be subject to financial penalties and other legal sanctions.

The FDAAA also further enhanced funding and power of the Office of Surveillance and Epidemiology, which is principally responsible for postmarketing safety monitoring within the FDA, elevating its role to a level on a par with the Office of New Drugs, which has the most thorough understanding of any approved drug within the FDA. The expectation is that these offices will more effectively collaborate on drug safety issues.

Finally, the FDAAA mandates efforts to modernize the Adverse Event Reporting System, to develop appropriate standards for evaluating such data in a timely manner, and to link the system to other large databases of drug-reaction reports collected by government and private organizations.

CONCLUSION

The history of the FDA shows that the agency is not a static organization. It continues to evolve in response to scientific advances, as well as social and political influences, with the neverending, but sometimes elusive goal of ensuring the safety and efficacy of drug therapies. Could an "elixir sulfanilamide" tragedy occur today? Readers may recognize diethylene glycol as the main ingredient of antifreeze. Tragically, cold syrup containing diethylene glycol killed dozens of individuals in Nigeria in 1990 and more than 100 individuals in Panama in 2006. Toothpaste, cold medicine, and other products containing diethylene glycol have been manufactured in China and distributed to many countries around the world, including the United States. Nurses should be aware of the historical events that have shaped and continue to influence the FDA, as part of a broad overview of the drug development process and the issues involved in introducing a drug to the market. This will provide background for next articles in this series, which will cover the ethical foundations of clinical research and the stages of drug development.

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Dr. Howland is Associate Professor of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania.

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Address correspondence to Robert H. Howland, MD, Associate Professor of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213; e-mail: HowlandRH@upmc.edu.