SECOND EDITION

FDA Regulatory Affairs

A Guide for Prescription Drugs, Medical Devices, and Biologics

Edited by
Douglas J. Pisano
David S. Mantus

informa
healthcare

FDA Regulatory Affairs

FDA Regulatory Affairs

A Guide for Prescription Drugs, Medical Devices, and Biologics

Second Edition

Edited by

Douglas J. Pisano

Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts, USA

David S. Mantus

Cubist Pharmaceuticals, Inc.
Lexington, Massachusetts, USA

informa
healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4200-7354-0 (Hardcover)
International Standard Book Number-13: 978-1-4200-7354-6 (Hardcover)

Library of Congress Cataloging-in-Publication Data

FDA regulatory affairs : a guide for prescription drugs, medical devices, and biologics / edited by Douglas J. Pisano, David S. Mantus. — 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-4200-7354-6 (hb : alk. paper)
ISBN-10: 1-4200-7354-0 (hb : alk. paper) 1. Drug development—United States. 2. United States Food and Drug Administration—Rules and practice. 3. Pharmaceutical industry—United States. I. Pisano, Douglas J. II. Mantus, David.
[DNLM: 1. United States. Food and Drug Administration. 2. Drug Industry—standards—United States. 3. United States Government Agencies—United States. 4. Biological Products—standards—United States. 5. Equipment and Supplies—standards—United States. 6. Government Regulation—United States. QV 1 F287 2008]
RM301.25.F37 2008
615′.19—dc22

2008014296

For Corporate Sales and Reprint Permissions call 212-520-2700 or write to: Sales Department, 52 Vanderbilt Avenue, 7th floor, New York, NY 10017.

Visit the Informa Web site at
www.informa.com

and the Informa Healthcare Web site at
www.informahealthcare.com

Preface

This book is a roadmap to the U.S. Food and Drug Administration and drug, biologic, and medical device development. It is written in plain English, with an emphasis on easy access to understanding how this agency operates with respect to the practical aspects of U.S. product approval. It is meant to be a concise reference that offers current, real-time information. It has been written as a handy reference for use by students, staff, and professionals at corporations, organizations, and schools and colleges across the United States in need of a simple, concise text from which to learn and teach. The topics in *FDA Regulatory Affairs: A Guide for Prescription Drugs, Medical Devices, and Biologics, Second Edition* are covered in a straightforward format. It is a compilation and commentary of selected laws and regulations pertaining to the development and approval of drugs, biologics, and medical devices in the United States. It is *not* intended to take the place of an actual reading of the *Laws of the United States of America* or the regulations of the U.S. Food and Drug Administration, it's agencies or any body that regulates the development or approval of drugs, biologics, and medical devices in the United States.

Douglas J. Pisano
David S. Mantus

Contents

Contributors

Josephine C. Babiarz MS Program in Regulatory Affairs, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, U.S.A.

Robert Blanks Idenix Pharmaceuticals, Inc., Cambridge, Massachusetts, U.S.A.

Bob Buckley Idenix Pharmaceuticals, Inc., Cambridge, Massachusetts, U.S.A.

Karen L. Drake Cubist Pharmaceuticals, Inc., Lexington, Massachusetts, U.S.A.

Vahé Ghahraman Regulatory Operations and Technology, Dyax Corporation, Cambridge, Massachusetts, U.S.A.

Alberto Grignolo PAREXEL Consulting, Lowell, Massachusetts, U.S.A.

Yolanda Hall Datafarm, Inc., Marlborough, Massachusetts, U.S.A.

Michael R. Hamrell MORIAH Consultants, Yorba Linda, California, U.S.A.

Timothy A. Keutzer Cubist Pharmaceuticals, Inc., Lexington, Massachusetts, U.S.A.

Steven R. Koepke SRK Consulting, LLC, Walkersville, Maryland, U.S.A.

Shylendra Kumar Datafarm, Inc., Marlborough, Massachusetts, U.S.A.

David S. Mantus Cubist Pharmaceuticals, Inc., Lexington, Massachusetts, U.S.A.

Christina A. McCarthy Cubist Pharmaceuticals, Inc., Lexington, Massachusetts, U.S.A.

Charles Monahan Regulatory Affairs, Molecular Insight Pharmaceuticals, Inc., Cambridge, Massachusetts, U.S.A.

Prabu Nambiar Vertex Pharmaceuticals, Inc., Cambridge, Massachusetts, U.S.A.

Tan T. Nguyen Food and Drug Administration, Center for Devices and Radiological Health, Rockville, Maryland, U.S.A.

Douglas J. Pisano School of Pharmacy, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, U.S.A.

Barry Sall PAREXEL Consulting, Waltham, Massachusetts, U.S.A.

1

Overview of FDA and Drug Development

Josephine C. Babiarz

MS Program in Regulatory Affairs, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, U.S.A.

Douglas J. Pisano

School of Pharmacy, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, U.S.A.

INTRODUCTION

A single agency, the Food and Drug Administration (FDA), regulates a trillion dollars of products, ranging from 80% of the U.S. food supply to all human health care products, electronic products that emit radiation, animal products, and cosmetics. In 2006, that agency approved 101 new drugs, 10 biologic license applications, and 39 devices under the premarket approval process and cleared 3217 devices[1] and recalled 4266 products in all categories.[2] That single agency is responsible for shellfish, stents, over-the-counter (OTC) cough syrups, tetanus shots, artificial sweeteners, mammography standards, prescription drugs, vitamins, and lipsticks, not to mention the readability of calorie and trans-fat information on a bag of potato chips. The economic impact of the FDA is difficult to calculate, the scientific challenges and increasing medical needs overwhelming, and the expectations contradictory.

The FDA is expected to protect us and our pets from harm, but allow us access to unproven therapies that might cure or benefit us. The FDA is to act

[1] See www.fda.gov/oc/FDA's 2006 Accomplishments/healthcare.html.

[2] See www.fda.gov/ora/about/enf_story/ch10/FY96toFY06Recalls.pdf.

quickly to get products to market, but must be right the first time, and is criticized as being too permissive or lax if a drug or device must be recalled later for safety concerns or unpredicted adverse events. Given the pace of scientific advancement, this is no small demand.

The FDA's authority and influence are the product of compromise, evolving over time. It is an agency that is governed as much by law as by science. History shows us that the FDA's authority has grown commensurate with the magnitude of harm suffered by the public because of the food and drugs consumed, as well as the devices used. The agency and its statutory framework remain a work in progress. To better understand the FDA, its controlling laws, and its role in public health, a brief summary is in order.

Regulations and laws are central social constructs that provide guidance for all societies around the globe. Governments create laws in a number of ways with various intents for a myriad of purposes. In the United States, laws are created by the Congress, a body of officials elected by the citizenry, who are charged with the governance of the country by representing the common, public good. The Congress proposes and passes laws that are relatively general in nature and intended to address some particular issue in a fashion that can be consistently applied by all who are affected by them. Once passed, laws are remanded to the appropriate government or administrative agency, which then decides on how these laws are to be applied. These "applications of law" are called regulations. Regulations serve as the practical foundation from which citizens adhere to the law as it was originally intended.

In the United States, all food, drugs, cosmetics, and medical devices for both humans and animals are regulated under the authority of the Food, Drug, and Cosmetic Act (FDCA), which in turn establishes the FDA. The FDA and all of its regulations were created by the government in response to the pressing need to address the safety of public with respect to its foods and medicinals. The purpose of this chapter is to describe and explain the nature and extent of these regulations as they apply to medical products in the United States. A historical perspective is offered as a foundation for regulatory context. In addition, the chapter will discuss the FDA's regulatory oversight and that of other agencies, the drug approval and development process, the mechanisms used to regulate manufacturing and marketing, as well as various violation and enforcement schemas.

THE EVOLUTION OF THE FDA—HOW THE PURE FOOD AND DRUG ACT BECAME THE FOOD AND DRUG ADMINISTRATION AMENDMENTS OF 2007

The History—1902 to 1972

Prior to 1902, the U.S. government took a hands-off approach to the regulation of drugs. Many of the drugs available were so-called patent medicines, which were so named because each had a more or less descriptive or patent name. No laws, regulations, or standards existed to any noticeable extent, even though the

United States Pharmacopoeia (USP) became a reality in 1820 as the first official compendium of the United States. The USP set standards for strength and purity, which could be used by physicians and pharmacists who needed centralized guidelines to extract, compound, and otherwise utilize drug components that existed at the time.[3]

However, in 1848, the first American drug law, the Drug Importation Act, was enacted when American troops serving in Mexico became seriously affected when adulterated quinine, an antimalarial drug, was discovered. This law required laboratory inspection, detention, and even destruction of drugs that did not meet acceptable standards. Later, in 1902, the Virus, Serum, and Toxins Act (Biologics Control Act) was passed in response to tetanus-infected diphtheria antitoxin, which was manufactured by a small laboratory in St. Louis, Missouri. Ten school children died as a result of the tainted serum. No national standards were as yet in place for purity or potency. The act authorized the Public Health Service to license and regulate the interstate sale of serum, vaccines, and related biologic products used to prevent or treat disease.

This act also spurred Dr. Harvey W. Wiley, chief chemist for the Bureau of Chemistry, a branch of the United States Department of Agriculture (USDA) and the forerunner for today's FDA investigate the country's foods and drugs. He established the Hygienic Table, a group of young men who volunteered to serve as human guinea pigs and who would allow Dr. Wiley to feed them a controlled diet laced with a variety of preservatives and artificial colors. More popularly known as the "Poison Squad," they helped Dr. Wiley gather enough data to prove that many of America's foods and drugs were "adulterated," the products' strength or purity was suspect or "misbranded," or the products had inadequate or inaccurate labeling. Dr Wiley's efforts, along with publication of Upton Sinclair's *The Jungle* (a book revealing the putrid conditions in America's meat industry), were rewarded when Congress passed America's first food and drug law, in 1906, the United States Pure Food and Drug Act (PFDA) (also known as the Wiley Act). The Wiley Act prohibited interstate commerce of misbranded foods or drugs based on their labeling. It did not affect unsafe drugs in that its legal authority would only come to bear when a product's ingredients were falsely labeled. Even intentionally false therapeutic claims were not prohibited.

This began to change in 1911 with the enactment of the Sherley Amendment, which prohibited the labeling of medications with false therapeutic claims that were intended to defraud the purchaser. These amendments, however, required the government to find proof of intentional labeling fraud. Later, in 1937, a sentinel event occurred that changed the entire regulatory picture. Sulfa became the miracle drug of the time and was used to treat many life-threatening infections. It tasted bad and was hard to swallow, which led

[3] Valentino J. Practical uses for the USP: a legal perspective. In: Strauss's Federal Drug Laws and Examination Review. 5th ed. Lancaster, PA: Technomic Publishing Co., 1999:38.

entrepreneurs to seek a palatable solution. S.E. Massingill Co. of Bristol, Tennessee, developed what it thought was a palatable, raspberry-flavored liquid product. However, it used diethylene glycol to solublize the sulfa. Six gallons of this dangerous mixture, Elixir of Sulfanilamide, killed some 107 people, mostly children.

The result was the passage of one of the most comprehensive statutes in the history of American health law. The federal Food, Drug, and Cosmetic Act of 1938 (FDCA), repealed the Sherley Amendments and required that all new drugs be tested by their manufacturers for safety and that those tests be submitted to the government for marketing approval via a new drug application (NDA). The FDCA also mandated that drugs be labeled with adequate directions if they were shown to have had harmful effects. In addition, the FDCA authorized the FDA to conduct unannounced inspections of drug manufacturing facilities. Though amended many times since 1938, the FDCA is still the broad foundation for statutory authority for the FDA as it exists today.

However, a new crisis loomed. Throughout the late 1950s, European and Canadian physicians began to encounter a number of infants born with a curious birth defect called "phocomeglia," a defect that resulted in limbs that resembled "flippers," similar to those found on seals. These birth defects were traced back to mothers who had been prescribed the drug thalidomide in an effort to relieve morning sickness while pregnant. The manufacturer of this drug applied for the U.S. marketing approval as a sleep aid. However, because of the efforts of Dr. Frances O. Kelsey, the FDA's chief medical officer at the time, a case was made that the drug was not safe and therefore not effective for release in the U.S. marketplace.

Dr. Kelsey's efforts and decisive work by the U.S. Congress resulted in yet another necessary amendment to the FDCA, in 1962, the Kefauver-Harris Act. This act essentially closed many of the loopholes regarding drug safety in American law. These "Drug Efficacy Amendments" now required drug manufacturers to prove safety and efficacy of their drug products, register with the FDA and be inspected at least every two years, have their prescription drug advertising approved by the FDA (this authority being transferred from the Federal Trade Commission), provide and obtain documented "informed consent" from research subjects prior to human trials, and increase controls over manufacturing and testing to determine drug effectiveness.

In an effort to address these new provisions of the act, the FDA contracted with the National Academy of Sciences along with the National Research Council to examine some 3400 drug products approved between 1938 and 1962 on the basis of safety alone. Called the Drug Efficacy Study Implementation Review of 1966 (DESI), it charged these organizations to determine whether post-1938 drug products were "effective" for the indications claimed in their labeling, or "probably effective," "possibly effective," or "ineffective." Those products not deemed effective were removed from the marketplace, reformulated, or sold with a clear warning to prescribers that the product was not deemed effective.

Later, in 1972, the FDA began to examine OTC drug products. Phase II of the Drug Efficacy Amendments required the FDA to determine the efficacy of OTC drug products. This project was much larger in scope than the analysis of prescription drugs. In the America of the 1970s, consumers could choose from more than 300,000 OTC drug products. The FDA soon realized that it did not have the resources to evaluate each and every one. Hence, the FDA created advisory panels of scientists, medical professionals, and consumers who were charged with evaluating active ingredients used in OTC products within 80 defined therapeutic categories. After examining both the scientific and medical literature of the day, the advisory panels made decisions regarding active ingredients and their labeling. The result was a "monograph" that described in detail acceptable active ingredients and labeling for products within a therapeutic class. Products that complied with monograph guidelines were deemed category I: safe and effective, not misbranded. However, products not in compliance with monograph guidelines were deemed category II: not safe and effective or misbranded. Category II products were removed from the marketplace or reformulated. Products for which data were insufficient for classification were deemed category III and were allowed to continue in the market until substantive data could be established or until they were reformulated and were in compliance with the monograph. The OTC Drug Review took approximately 20 years to complete.

Although there were numerous other federal laws and regulations that were passed throughout the 1970s, many were based on regulating the professional practice of medical professionals or for the direct protection of consumers. For example, the federal Controlled Substances Act (CSA), part of the Comprehensive Drug Abuse and Prevention Act of 1970, placed drugs with a relatively high potential for abuse into five federal schedules along with a "closed record keeping system," designed to track federally controlled substances via a definite paper trail, as they were ordered, prescribed, dispensed, and utilized throughout the health care system.

1980—2004: AIDS, Orphans, Terrorism, and Economic Incentives

The 1980s also passed with significant regulatory changes. Biotechnology had begun on a grand scale and the pharmaceutical industry was on its cutting edge. Many of the medicinal compounds being discovered were shown to be very expensive and have limited use in the general U.S. population. However, these compounds could prove lifesaving to demographically small patient populations who suffered from diseases and conditions that were considered rare. In an effort to encourage these biotech pharmaceutical companies to continue to develop these and other products, Congress passed the Orphan Drug Act in 1983. The Act continues to allow manufacturers incentives for research, development, and marketing of drug products used to treat rare diseases or conditions that would otherwise be unprofitable via a system of market exclusivity, and substantial breaks and deductions in a manufacturer's corporate taxes. Though the success

of the Orphan Drug Act proved of great medical benefit for a few, a scandal was looming in other parts of the pharmaceutical industry.

The generic pharmaceutical industry experienced steady growth as many of the exclusive patents enjoyed by major pharmaceutical companies for brand-named products were beginning to expire. Generic versions of these now freely copied products were appearing much more frequently in the marketplace. However, these generic copies were required to undergo the same rigorous testing that brand name, pioneer, or innovator products did, thereby increasing costs, duplicating test results, and substantially slowing the availability of less expensive but equivalent drugs. To speed access to cheaper therapies, Congress passed the Price Competition and Patent Restoration Act in 1984. This Act, also called the Waxman-Hatch Act after its sponsors, was designed to level the playing field in the prescription drug industry with regard to patent-protected prescription drug products and their generic copies.

The Waxman-Hatch Act was composed of two distinct parts or "titles." Title I was for the benefit of the generic pharmaceutical industry. It extended the scope of the Abbreviated NDA (ANDA) to cover generic versions of post-1962–approved drug products. It required that generic versions of pioneer or innovator drugs have the same relevant aspects as those with regard to bio-equivalence (rate and extent of absorption of the active drug in the human body) and pharmaceutical equivalence (same dosage form as the pioneer drug to which it is compared). Though somewhat simplified, the Waxman-Hatch Act permitted easier market access to generic copies of pioneer drugs, provided they were not significantly different from the pioneer drug in their absorption, action, and dosage form. In addition, Title II of the act was designed to aid and encourage research-based or innovator pharmaceutical companies in continuing their search for new and useful medicinal compounds by extending the patent life of pioneer drug products to compensate for marketing time lost during the FDA "review period."[4]

While the patent extension benefit has become somewhat moot because of an overall reduction in the FDA review time as a result of prescription drug user fees, the value of patent-protected drugs has skyrocketed, with so-called block-buster drugs garnering millions of dollars in sales in less than a year. Market exclusivity and patent extensions remain powerful motivators used to encourage orphan drug development and, as discussed below in the section "The Food and Drug Administration Amendments Act of 2007," pediatric testing.

Congress recognized that counterfeit drugs, as well as improper control over drug samples, and sales and marketing materials posed serious health

[4] No federal agency, including the FDA, can compel the manufacture of generic drugs once patent rights have expired. In recent times, the Waxman-Hatch Act has come under criticism for that reason. Under a free market system, companies that hold expired patents may, and some do, make "reverse payments" to potential competitors to keep generic drugs off the market. This practice clearly frustrates the spirit of the law; however, it is legal.

hazards. Accordingly, the Prescription Drug Marketing Act of 1988 requires that all drugs be distributed through legitimate commercial channels, that pharmaceutical sales representatives maintain detailed accounts of drug samples (giving birth to the term "detailer"), and that importation of drugs from foreign countries be restricted.[5]

Nineteen ninety was a year when Congress focused on devices and nutrition. The Safe Medical Devices Act of 1990 established a user reporting system to improve device safety. If a medical device probably caused or contributed to death, serious injury, or illness, representatives of the institution or facility where the incident occurred were required to file a report with the FDA. In turn, the device manufacturers were required to address or respond to the incident. The statute also gives FDA the power and authority to recall devices,[6] which it does not have in the case of drugs (drug recalls are voluntary actions by the manufacturers; FDA can and will seize drug lots, however). This Act also addressed combination products, establishing that the jurisdiction of the FDA centers would be based on the primary indication of the product. Nineteen ninety also brought regulation to food; the Nutrition Labeling and Education Act requires nutrition labeling and health claims to be consistent with the format and rules established by the FDA. This law brought new—and uniform—meaning to the words "low fat" and "light."[7]

Nineteen ninety-two saw three major laws enacted. An unintended side effect of the Waxman-Hatch Act was a very public scandal in which a few unscrupulous generic pharmaceutical companies took shortcuts in reporting data, submitted fraudulent samples, and offered bribes to the FDA officials to gain easy and rapid market approval of their products.[8] The Generic Drug Enforcement Act provided for debarment and other serious penalties for bribery, fraud, or misconduct, among other deterrents.[9] Congress also strengthened device oversight; the Medical Device Amendments of 1992 added penalties if a manufacturer did not comply with postmarketing surveillance testing and reporting.[10]

---

[5] Prescription Drug Marketing Act of 1988; Public Law 100–23. See www.fda.gov/opacom/backgrounders/miles.html.

[6] Ibid.

[7] Ibid.

[8] Sec. 306(k) of the FDCA [21 USC 335a(k)] requires that drug product applicants certify that they did not and will not use in any capacity the services of any debarred persons in connection with a drug product application. See www.fda.gov/cder/guidance/1700dft.pdf. Note that this certification applies to combination products that include any drug component; this certificate is commonly used by device manufacturers as well.

[9] Generic Drug Enforcement Act of 1992; Public Law 102–282; See www.fda.gov/ora/compliance_ref/debar/297_debar.htm.

[10] See http://thomas.loc.gov/cgi-bin/bdquery/z?d102:SN02783:@@@D&summ2=m&|TOM:/bss/d102query.html.|

The most significant change of that year came in the form of the first Prescription Drug User Fee Act (PDUFA).[11] The Act was intended to help the FDA generate additional funds to upgrade and modernize its operations and to accelerate drug approval. It authorized FDA to charge pharmaceutical manufacturers a "user fee" to accelerate drug review. These funds in turn are used by the FDA. Critics and supporters alike quickly point out that the user fee is fully paid when the FDA approves a product—not if the final clinical results do not prove the benefit outweighs the risk. This fee assessment has sparked a great deal of debate about the real conflict of interest present when the FDA reviewers are examining a product whose approval fees go directly to fund the reviewers' employment. As will be discussed later, there are checks and balances in this system, as Congress appropriates funds to cover FDA administration, including reviewers' salaries.

As a result of PDUFA, FDA has hired more personnel and reduced approval time of new pharmaceutical products from greater than 30 months to approximately 13 to 15 months today. However, the first act had a "sunset" provision, which limited FDA's authority to charge user fees to the year 1997. The Act was so successful that PDUFA has been reauthorized and extended three additional times, and the fee concept has been expanded to include medical devices and biologics (Medical Device User Fee and Modernization Act of 2002, MDUFMA),[12] as well as voluntary review fees for television advertisements. The most recent reauthorization, PDUFA IV, is part of the Food and Drug Administration Amendments Act of 2007, discussed at length below.

Congress relaxed the regulation of certain industries. The Dietary Supplement Health and Education Act (DSHEA) of 1994 shifted the burden of proof from industry to the FDA. For drugs, devices, and biologics, a sponsor or manufacturer must prove that the product is safe and effective for the indication claimed. The opposite is true of dietary supplements; thanks to this law, FDA "bears the burden of proof . . . to show that a dietary supplement is adulterated."[13]

Congress continued to expand and enhance the scope and powers of the FDA. One example is the FDA Modernization Act (FDAMA) of 1997.[14] FDMA not only extended user fee provisions but also waived some fees for small companies and for developers of orphan products, manufacturers of pediatric applications, and certain biologics. FDAMA also gave FDA authority to conduct "fast track" product reviews to speed lifesaving drug therapies to market, permitted an additional six-month patent exclusivity for pediatric prescription drug products and required the National Institutes of Health (NIH) to build a

[11] Public Law 102–571; 21 USC 379g and ff.

[12] Public Law 107–250; 21 USC 379F et seq.

[13] See www.fda.gov/opacom/laws/dshea.htmo#sec4.

[14] Public Law 105–115; 21 USC 301 et seq.

publicly accessible database on clinical studies of investigational drugs or life-threatening diseases.

FDAMA addressed the real dilemma of terminally ill patients, who were routinely denied access to experimental drugs because of the lack of safety and efficacy data on the drugs; FDA had no authority to allow the use of such drugs outside enrollment in a controlled clinical investigation. However, pressures from acquired immunodeficiency syndrome (AIDS) activists in particular moved Congress to change the rules. Under FDAMA, there was expanded access to unapproved drug and devices, specifically therapies and diagnostics for serious diseases or life-threatening conditions.[15] Individuals not enrolled in a formal clinical trial could obtain unapproved products—i.e., products covered by an investigational new drug (IND) or investigational device exemption (IDE)—during emergencies or for personal use. Unapproved drugs are available under "expanded access" or "compassionate use,"[16] experimental devices are available under the humanitarian device exemptions.[17]

FDAMA addressed, albeit briefly, issues of "off-label" promotion. Generally, a manufacturer may only advertise those claims and indications that are stated in the label; any deviation can be prosecuted as misbranding.[18] FDA took the position that certain publications directed at prescribers were in fact off-label promotion. Various critics, including the Washington Legal Foundation, felt that this position violated the right of freedom of speech, guaranteed by the First Amendment to the United States Constitution. A federal court agreed with the foundation,[19] and Congress was forced to address the issue. The fundamental question was and remains how can the public be adequately protected if a manufacturer is allowed to promote all the uses of a product and not only those that FDA has determined to be supported by scientific evidence?

The compromise Congress crafted was to allow dissemination of information on unapproved uses of products to a limited group of professionals—i.e., physicians, insurance companies, and other health care practitioners. This provision has expired,[20] and the battlefront has shifted to the arena of post-marketing surveillance and drug database registries, discussed below in the section "The Food and Drug Administration Amendments Act of 2007."

Imitation is the sincerest compliment—the success of PDUFA gave birth to the Medical Device User Fee and Modernization Act (MDUFMA) in 2002. MDUFMA was enacted "in order to provide the FDA with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical

[15] See 21 USC section 360bbb and following.

[16] See www.fda.gov/cder/guidance/3647fnl.pdf.

[17] See www.fda.gov/cdrh/ode/guidance/1381.html.

[18] See 21 USC section 331 and following.

[19] See Washington Legal Foundation v. Henney; Federal Appellate District DC US Court of Appeals, Decided Feb 11, 2000; No. 99-5304.

[20] See 21 USC section 360aaa and following.