CHAPTER OBJECTIVES

Upon completing this chapter, the reader will be able to:

- Identify the significant historical events that have shaped the current federal Food, Drug and Cosmetic Act (FDCA).
- Distinguish among the definitions of food, drug, dietary supplement, cosmetic, device, label, and labeling.
- Recognize the prohibited acts, penalties, and enforcement mechanisms in the FDCA.
- Identify the situations that may cause a drug to be adulterated or misbranded.
- Differentiate FDCA requirements for prescription drugs from those for over-the-counter drugs.
- Understand the issues and procedures pertaining to new drug approval.
- Describe the legal requirements for manufacturers that advertise prescription drugs to health care professionals and consumers.

The federal Food, Drug and Cosmetic Act (FDCA) (21 U.S.C. § 301 et seq., 52 Stat. 1040 (1938)) provides for the comprehensive regulation of all drugs introduced into interstate commerce. The intent of the law is to protect consumers from adulterated or misbranded foods, drugs, cosmetics, or devices. Under the act, no new drug may be marketed and sold unless it has been proved both safe and effective for its intended use and approved by the federal Food and Drug Administration (FDA).

This chapter discusses relevant history, definitions, and provisions of the FDCA related to the development, production, and marketing of products, from the discovery of a new concept by a scientist to the delivery of a therapeutically appropriate product to a pharmacy. Chapter 3 describes how those products are regulated once they reach the pharmacy from which they will be dispensed. In many sections of these chapters, the reader will note that the applicable law is either cited or summarized first, followed by an explanation of the law from the perspective of the author.
Historical Overview of the Federal Food, Drug and Cosmetic Act

In order to protect public health, governments of nearly every civilization have sought to protect the public from adulterated food products. More modern laws in the U.S. in the 1800s against the adulteration of foods and drugs were led by two factors. One, advances in analytical chemistry and microscope technology, and two, studies showing the impact of adulterated foods and drugs on human life. One such study in 1850 showed that average life expectancy actually decreased by as many as seven years over certain periods of time in Boston and New York in part because of adulterated drugs and foods. (See Hyman, 2002, Chapter 2.)

Our present-day food and drug regulatory system in the U.S., represented by the FDCA, has been shaped by several important amendments and events and warrants a brief historical discussion at this point. The purpose of this historical overview is to provide the reader a general background of the act. Many of the amendments and events chronicled here are discussed in greater detail later in this chapter and in Chapter 3.

Pure Food and Drug Act of 1906

At the turn of the century, investigative reports revealed widespread food and drug adulteration problems. Most notably, the 1906 novel, The Jungle, by Upton Sinclair, described atrocious adulteration problems in the meat industry. Concern for the risks to public health and safety associated with unsanitary and poorly labeled foods and drugs prompted Congress in 1906 to pass the Pure Food and Drug Act (34 Stat. 768). The law prohibited the adulteration and misbranding of foods and drugs in interstate commerce. It fell short of providing the protection that Congress intended, however, because a 1911 U.S. Supreme Court decision, United States v. Johnson, 221 U.S. 488, held that the misbranding provision in the law did not prevent false or misleading efficacy claims. In Johnson, the manufacturer claimed on the label that the drug was effective against cancer, knowing that this representation was false. The Court ruled that the misbranding provision in the law prevented false statements only as to the drug’s identity (i.e., strength, quality, and purity). Some manufacturers, fearing a violation of the labeling provision, simply omitted information from the label because the act did not require the label to list the ingredients, include directions for use, or provide warnings. Moreover, the act failed to regulate cosmetics or devices.

The Johnson decision prompted Congress to amend the Pure Food and Drug Act in 1912 to prohibit false and fraudulent efficacy claims. Even with this amendment, however, the act failed to achieve its purpose. The amendment was difficult to enforce because it required the government to prove fraudulent intent on the part of one who made false statements on the label. By pleading ignorance, violators could escape enforcement.

Despite public awareness that the 1906 law was inadequate, there was no new legislation until 1938. By that time, pressure for a new law had been building for many years. A catalyst for the new law was the sulfanilamide elixir tragedy of 1937. Sulfanilamide was one of the first of the “miracle” anti-infective sulfa drugs marketed. A manufacturer who sought to produce the drug in an elixir form seized upon diethylene glycol as the best solvent. (Diethylene glycol is today used as an industrial solvent and for other industrial uses.) No toxicity tests had been done, despite the fact that little was known about the use of diethylene glycol in humans. The solvent proved to be a deadly poison, and 107 deaths were ultimately attributed to this elixir. The 1906 law had not granted the FDA the authority to ban unsafe drugs, so the FDA had to remove the product on the basis of a technical misbranding violation—that an elixir must contain alcohol, and the product did not.
Food, Drug, and Cosmetic Act of 1938

The FDCA of 1938 (21 U.S.C. § 301 et seq. 52 Stat. 1040), with amendments, forms the nucleus of today’s law. All the amendments and laws described subsequently in this section are amendments to the 1938 act. It provided that no new drug could be marketed until proven safe for use under the conditions described on the label and approved by the FDA. The law also expanded the definitions of misbranding and adulteration used in the earlier act, requiring that labels must contain adequate directions for use and warnings about the habit-forming properties of certain drugs. The 1938 law applies to cosmetics and devices as well. Significantly, however, the act exempted drugs marketed before 1938 from the requirement that new drugs be proven safe before being marketed.

In 1941, the FDCA was amended to allow the FDA to require batch certification of the safety and efficacy of insulin to ensure uniform potency. Because of concern over the quality of penicillin production, the FDCA was amended to allow the FDA to require batch certification of the safety and efficacy of penicillin in 1945. Subsequent amendments extended the certification requirement to other antibiotic drugs or any derivative of an antibiotic drug. (In 1997, the Food and Drug Administration Modernization Act eliminated the batch certification requirement for insulin and antibiotics.)

In 1948, the extent of the FDCA’s jurisdiction was challenged in United States v. Sullivan, 332 U.S. 689, which was discussed in Chapter 1. The defendant pharmacist contended that federal law did not apply to his acts because his acts only affected intrastate transactions. The Supreme Court of the United States, however, declared that the jurisdiction of the act extends to transactions between the pharmacist and the patient. Therefore, the FDCA applies to drugs held for sale in a pharmacy.

Durham-Humphrey Amendment of 1951

The 1938 FDCA required all drugs to be labeled with “adequate directions for use.” When the act was passed, however, many drugs on the market were not safe for use except under medical supervision. These drugs could not meet the “adequate directions for use” requirement. The Durham-Humphrey Amendment (also often referred to as the Prescription Drug Amendment) was enacted in 1951 (65 Stat. 648) to solve this problem. The amendment established two classes of drugs, prescription and over the counter, and provided that the labels of prescription drugs need not contain “adequate directions for use” so long as they contain the legend, “Caution: Federal law prohibits dispensing without a prescription.” When dispensed by a pharmacist, inclusion on the label of directions from the prescriber satisfies the “adequate directions for use” requirement.

In addition to establishing the two classes of drugs, the amendment also authorizes oral prescriptions and refills of prescription drugs. Because the Durham-Humphrey Amendment deals primarily with the dispensing of medications, rather than with the development and marketing of them, it is discussed extensively in Chapter 3.

Food Additives Amendment of 1958

After several years of hearings, Congress amended the FDCA to require that components added to food products must receive premarket approval for safety (P.L. 85-929). The law also contains an anticancer provision, commonly known as the Delaney Clause, which prohibits the approval of any food additive that might cause cancer.

Color Additive Amendments of 1960

In 1960, Congress amended the FDCA to require manufacturers to establish the safety of color additives in foods, drugs, and cosmetics. Under the Color Additive Amendments, the FDA can approve
a color for one use but not for others (e.g., external use only). The amendments also contain a Delaney Clause, similar to the one contained in the Food Additives Amendment.

**Kefauver-Harris Amendment of 1962**

In the late 1950s, a popular sedative, thalidomide, was being marketed in Europe. The William S. Merrell Company distributed the drug experimentally in the United States in 1960, but the FDA withheld final approval of the new drug application (NDA) pending additional safety information. In 1961, it was confirmed that the drug had caused a birth defect, phocomelia (seal limbs), in thousands of infants. Because the FDA had refused to allow the marketing of thalidomide in the United States, the number of birth defects caused by the drug in this country was low. Nonetheless, the worldwide disaster caused Congress to enact the Kefauver-Harris Amendment to the FDCA.

This amendment, also called the Drug Efficacy Amendment (76 Stat. 780), strengthened the new drug approval process by requiring that drugs be proved not only safe, but also effective. The efficacy requirement was made retroactive to all drugs marketed between 1938 and 1962. The amendment also:

- Transferred jurisdiction of prescription drug advertising from the Federal Trade Commission (FTC) to the FDA
- Established the Good Manufacturing Practices (GMP) requirements
- Added more extensive controls for clinical investigations by requiring the informed consent of research subjects and reporting of adverse drug reactions

**Medical Device Amendments of 1976**

Under the 1938 Act, the FDA had no authority to review medical devices for safety and efficacy before marketing. As a result, the agency resorted to classifying devices as drugs when it deemed appropriate and necessary. Prompted by public safety concerns with certain devices such as the Dalkon Shield, an intrauterine device, Congress amended the FDCA in 1976 to provide for more extensive regulation and administrative authority regarding the safety and efficacy of medical devices. The Medical Device Amendments (P.L. 94-295; 90 Stat. 539) require:

- Classification of devices according to their function
- Premarket approval
- Establishment of performance standards
- Conformance with GMP regulations
- Adherence to record and reporting requirements

**Orphan Drug Act of 1983**

For years, pharmaceutical manufacturers had urged Congress to recognize that the NDA process was too expensive to warrant the development and marketing of drugs for diseases that affect relatively few people. In fact, the FDA acknowledged that between 1973 and 1983 only 10 products were approved for the treatment of rare diseases. In response, Congress passed the Orphan Drug Act (P.L. 97-414) in 1983 to provide tax and exclusive licensing incentives for manufacturers to develop and market drugs or biologicals for the treatment of “rare diseases or conditions” (defined as those affecting fewer than 200,000 Americans). Between the act’s passage and the year 2000, the FDA approved about 172 orphan drugs and biological products, and 700 additional orphan-designated products were being developed.
Drug Price Competition and Patent Term Restoration Act of 1984

Also called the Waxman-Hatch Amendment, the Drug Price Competition and Patent Term Restoration Act (P.L. 98-417) was enacted in 1984 to streamline the generic drug approval process while giving patent extensions, in certain cases, to innovator drugs. The intent of the law is to make generic drugs more readily available to the public and, at the same time, provide incentives for manufacturers to develop new drugs. The law is the result of intense lobbying and negotiating between generic drug manufacturers and the manufacturers of innovator drugs.

Prescription Drug Marketing Act of 1987

Congress enacted the Prescription Drug Marketing Act (P.L. 100-293) in 1987 in response to growing alarm that a secondary or diversionary distribution system for prescription drugs was threatening the public health and safety and creating an unfair form of competition. This law establishes sales restrictions and recordkeeping requirements for prescription drug samples. It also prohibits hospitals and other health care entities from reselling their pharmaceutical purchases to other businesses and requires the state licensing of drug wholesalers.

Safe Medical Devices Act of 1990

This act further strengthened the Medical Devices Amendment Act of 1976, giving the FDA additional authority especially related to postmarketing requirements and premarket notification and approval, while at the same time expediting the premarket device approval process.

The Generic Drug Enforcement Act of 1992

This act warrants discussion to highlight a scandal that occurred when some FDA staff accepted bribes from generic drug industry personnel in order to facilitate the approval process of certain generic drug products. These individuals were convicted and the scandal prompted Congress to pass this law authorizing the FDA to ban individuals or firms from participating in the drug approval process if convicted of related felonies. The law also imposes severe civil penalties for any false statements, bribes, failures to disclose material facts, and other related offenses.

Prescription Drug User Fee Act of 1992

Although the FDA was called on to review an ever-increasing number of drugs for approval, it found Congress unwilling to expand its budget. Instead, the administration and Congress took the approach that private industry should shoulder part of the costs for new drug approval rather than the taxpayers. Thus, Congress passed the Prescription Drug User Fee Act (PDUFA), which requires manufacturers to pay fees for applications and supplements when the FDA must review clinical studies (P.L. 102-571). The fees provide the FDA with the resources to hire more reviewers to assess these clinical studies and hopefully speed up the NDA reviews.

Nutrition Labeling and Education Act of 1990

Capitalizing on increased consumer interest in health and nutrition, the 1980s witnessed many food companies promoting their food products with nutritional claims. Congress enacted the Nutrition Labeling and Education Act (NLEA) (P.L. 101-535) to encourage this trend. The NLEA mandates nutrition labeling on food products and authorizes health claims on product labeling, as long as they are made in compliance with FDA regulations.
Dietary Supplement Health and Education Act of 1994

Dietary supplement manufacturers felt that the NLEA left too much authority with the FDA and unduly restricted the promotion of dietary supplements. As a result, Congress was persuaded to pass the Dietary Supplement Health and Education Act (DSHEA) (P.L. 103-417) to define dietary supplements and permit manufacturers to make certain claims that otherwise would have been illegal under the FDCA. The DSHEA in essence forced the FDA to regulate dietary supplements more as foods than as drugs.

Food and Drug Administration Modernization Act of 1997

FDA critics, which included drug manufacturers, Congress, and consumer groups, believed that the FDA was not efficiently administering its statutory responsibilities and that the FDCA itself produced too burdensome a regulatory system for drug approval. The Food and Drug Administration Modernization Act of 1997 (FDAMA) was passed primarily to streamline regulatory procedures to ensure the expedited availability of safe and effective drugs and devices.

Building on the Prescription Drug User Fee Act, FDAMA increases the FDA’s public accountability, requires an FDA mission statement to define the scope of its responsibilities, and requires the agency to publish a compliance plan in consultation with industry representatives, scientific experts, health care professionals, and consumers. The intent is to eliminate backlogs in the approval process and ensure the timely review of applications. In particular, the FDAMA creates a fast-track approval process for drugs intended for serious or life-threatening diseases, establishes a databank of information on clinical trials, authorizes scientific panels to review clinical investigations, and expands the rights of manufacturers to disseminate unlabeled use information.

The FDAMA also expands the FDA’s authority over over-the-counter (OTC) drugs and establishes ingredient-labeling requirements for inactive ingredients. States are preempted from establishing labeling requirements for OTC drugs and cosmetics when federal requirements exist. The law also affects the regulation of medical devices in part by mandating priority review for breakthrough technologies in medical devices and allowing the FDA to contract with outside scientific experts for review of medical device applications.

Rationale for Federal Drug Regulation

The primary goal of the Pure Food and Drug Act of 1906 and the succeeding drug-related legislation was the protection of the public welfare. Few can deny that the public should be protected or that government should play a role in the protective effort. Nonetheless, there is a legitimate concern by some that government may go too far in protecting people from the consequences of their own risky choices.

The development of federal drug regulation shows a pattern of increasing government intrusion into the decisions of the people who use drugs. The 1906 law was an example of “indirect regulation.” Its purpose was to help people make their own decisions by providing accurate and useful information through appropriate labeling. The 1938 act reinforced the indirect regulation by expanding the labeling requirements, but it also introduced an important piece of “direct regulation” by keeping off the market those drugs that have not met government safety standards. This type of regulation is direct because it makes decisions for people rather than helping them to make decisions for themselves. The 1951 and 1962 amendments increased direct regulation by mandating prescriptions for certain drugs and requiring proof of efficacy, as well as safety for drug approval. At present, most of the drugs available cannot be used unless the government has certified them as safe and effective and another person (an authorized prescriber) has decided to permit their use.
Against this background of increasingly paternalistic drug laws, modern-day consumers have developed an independence regarding therapeutic choices and have matured in their ability to make sophisticated decisions for themselves. It is perhaps no coincidence that the Omnibus Budget Reconciliation Act of 1990 (OBRA-90) (P.L. 101-508), one of the latest major federal drug laws, focuses on informed decisions by patients rather than on decisions by government or health care providers on behalf of patients. (See Chapter 6 for more information.) It also is perhaps no coincidence that the past 20 years or so have witnessed an unprecedented number of drugs switched from prescription status to OTC status. This may signal the beginning of a trend away from direct regulation and back toward indirect regulation, empowering patients to participate actively in health care decisions rather than passively accepting therapies decided on by others.

The Food and Drug Administration (FDA)

Because primary enforcement of the FDCA is vested in the FDA, it is important to know a little about the agency. The FDA is a component of the Department of Health and Human Services (DHHS), and actual authority for administering the FDCA is really vested with the secretary of DHHS. In fact, until 1988 the secretary appointed the commissioner of the FDA. The act now directs the president to appoint the commissioner with the confirmation of the Senate; however, the commissioner still remains accountable to the secretary. In reality, the secretary has delegated most of the secretary's authority to the commissioner, who in turn has delegated the majority of authority to various FDA directors. The FDA’s website can be accessed at www.fda.gov.

The agency is structured around the concept of the national headquarters providing policy and decision making, together with an extensive field force of professionals throughout the country to provide additional decision-making and regulatory enforcement. At the headquarters level, five centers share the authority for scientific and regulatory evaluations and interpretations:

- Center for Biologics Evaluation and Research
- Center for Food Safety and Applied Nutrition
- Center for Drug Evaluation and Research
- Center for Veterinary Medicine
- Center for Devices and Radiological Health

Each center has a director and several managers. The field is divided into 6 geographic regions with 20 district offices. The district offices provide inspections and work cooperatively with state and local agencies and provide source information to headquarters.

Because the FDA is an administrative agency, as discussed in Chapter 1, it has rulemaking authority (Section 707 of the FDCA). In fact, the FDA prefers to regulate by regulation if at all possible. But, the agency also may pursue a less formal avenue by publishing guidance documents. The purpose of guidance documents is to clarify laws or regulations, to explain how compliance with the laws or regulations may be achieved, and to outline review and enforcement approaches. The FDA has issued several guidance documents, some of which will be referred to in this book. Guidance documents are not legally binding, nor legally enforceable. Nonetheless, these guides represent the agency’s best thinking upon a particular subject and should be followed.

Although the FDA is staffed with considerable scientific expertise, it also regularly relies on advice from outside experts in the form of standing advisory committees. Most members of these committees are physicians, but they also include nurses, pharmacists, statisticians, epidemiologists, and other professionals. Members are recruited through the Federal Register, and often are nominated by
professional organizations and professional schools. The secretary of DHHS makes the final selec-
tion of members from the list of nominees. Committee size ranges from 9 to 15 members. Although
the FDA is not obligated to follow a committee recommendation, it often does.

**Defining and Distinguishing Drugs from Foods, Dietary Supplements,
Devices, and Cosmetics**

**The Law**

Section 201 of the FDCA (21 U.S.C. § 321) provides definitions for the important terms used in the
act. Understanding these definitions is critical to understanding the FDCA.

(f) The term “food” means (1) articles used for food or drink for man or other animals, (2) chewing gum,
and (3) articles used for components of any such article. (§ 201(f); 21 U.S.C. § 321(f))

(g) (1) The term “drug” means (A) articles recognized in the official United States Pharmacopoeia, official
Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any
of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of dis-
ease in man or other animals; and (C) articles (other than food) intended to affect the structure or any func-
tion of the body of man or other animals; and (D) articles intended for use as a component of any articles
specified in clause (A), (B), or (C).

(2) The term “counterfeit drug” means a drug which, or the container or labeling of which, without author-
ization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness
thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in
fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is rep-
resented to be the product of, or to have been packed or distributed by, such other drug manufacturer,
processor, packer, or distributor. (§ 201(g); 21 U.S.C. § 321(g))

(h) The term “device”... means an instrument, apparatus, implement, machine, contrivance, implant, in
vitro reagent, or other similar or related article, including any component, part, or accessory, which is

(1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supple-
ment to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treat-
ment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does
not achieve any of its principal intended purposes through chemical action within or on the body of
man or other animals and which is not dependent upon being metabolized for the achievement of any
of its principal intended purposes. (§ 201(h); 21 U.S.C. § 321(h))

(i) The term “cosmetic” means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, intro-
duced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promot-
ing attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such
articles, except that such term shall not include soap. (§ 201(i); 21 U.S.C. § 321(i))

**Explanation of the Law**

Ask people about their perception of a drug and they will likely respond that it is a chemical entity
for introduction into the body in one manner or another to improve one’s health. The legal defini-
tion of drug (see subsection g above), however, in the FDCA leaves little doubt that Congress intended the term *drug* to have a much broader meaning than that, broader even than any scientific or medical definition. Note that subsection g uses the term *articles* to describe a drug. Articles can include chemical and nonchemical entities, and in fact most anything. Part B of the drug definition addresses products intended for use with diseases, whereas part C recognizes that even products not intended for use with diseases may still be drugs if they make a structure or function claim. For example, a product claimed by a manufacturer to prevent pregnancy may not be a drug under part B (because pregnancy is not a disease), but may be a drug under part C (because preventing pregnancy means that the product intends to affect the function of the body).

The FDA has used the drug definition to its advantage on several occasions by adjudicating an article to be a drug and then removing it from the market for failing to meet the premarket approval required of new drugs. Establishing that an article is a drug, as opposed to say a food, dietary supplement, or cosmetic, provides the agency with considerably more authority over the article.

The crucial issue in the determination of whether a product is a drug centers on whether the supplier made a therapeutic or health claim, or a structure/function claim. In other words, was the article intended to diagnose, cure, mitigate, treat, or prevent a disease, or (for articles other than food) was it intended to affect the body structure or function? The fact that a supplier, even in good faith, does not believe that its product is a drug or does not want its product to be a drug has little relevance. If therapeutic or structure/function claims are made, an article is a drug, no matter what disclaimers may be included in the labeling. Thus, a supplier cannot mitigate a therapeutic or structure/function claim for a product by proclaiming that the product is not a drug. For example, assume that a company that manufactures alfalfa pellets for animals decides to produce alfalfa tablets for humans, claiming that the tablets will cure ulcers and other gastrointestinal disorders. The label specifically notes that the tablets are not drugs. On the basis of the therapeutic claims, however, a court is likely to consider the product a drug, even though the manufacturer says it is not, and even though alfalfa by itself is certainly not a drug.

As a distinction, it is the supplier’s intended use of the product that is important, not the purchaser’s intended use. The mere use of an article for therapeutic purposes by purchasers, where the supplier does not intend the product to be used therapeutically or makes no therapeutic claims, does not usually make the product a drug. Health food stores and pharmacies have hundreds of examples of these types of products on their shelves. Similarly, although some hardware stores sell dimethyl sulfoxide (DMSO) as an industrial solvent and some purchasers apply it externally to reduce joint pain, this use does not make it a drug.

In contrast, some products that contain entities normally considered drugs might not be drugs. For example, in the case of *Action on Smoking and Health v. Harris*, 655 F.2d 236 (D.C. Cir. 1980), a public interest group sought to have cigarettes declared drugs on the ground that they contain nicotine. The FDA, however, determined that the drug definition applies only to those brands of cigarettes about which a vendor makes therapeutic claims, and the court supported the FDA’s position. Changing its position in the 1990s, the FDA asserted that nicotine is a drug and that cigarettes and smokeless tobacco are drug-delivery devices. The agency found that tobacco products are intended to satisfy addiction, stimulation and tranquilization, and weight control. As a result, the FDA issued a regulation in 1996 intended to reduce tobacco consumption among children and adolescents (61 Fed. Reg. 44397). Tobacco manufacturers, retailers, and advertisers challenged the FDA arguing that the agency lacks authority to regulate tobacco products. In a 5 to 4 decision, the U.S. Supreme Court agreed with the plaintiffs, finding that Congress intended to exclude tobacco from the FDA’s jurisdiction (*Food and Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000)).
Although courts interpret the definition of the term drug broadly and often defer to the expertise of the FDA, the agency does not always prevail. In *National Nutritional Foods Association v. Mathews*, 557 F.2d 325 (2nd Cir. 1977), the FDA was unsuccessful in its attempt to classify vitamins A and D in high dosages as drugs, on the basis of a lack of nutritional value and potential toxicity. The court held that nutritional value and toxicity were not relevant to the statutory definition of a drug.

A court will admit evidence of therapeutic intent from sources other than the labeling of the product. Thus, therapeutic claims that the manufacturer made while advertising on radio or television, or in newspapers or brochures, will be considered evidence that a product is a drug. Moreover, the fact that a product is being marketed as an injection, capsule, or tablet may add evidence of therapeutic intent, despite the absence of therapeutic language in the labeling.

**Foods Versus Drugs**

The distinction between food and drug has become an important issue, especially in view of the proliferation and popularity of natural products, dietary supplements, and other “health food” type products. As you likely surmised from the previous discussion, almost any food might be considered a drug if a therapeutic or health claim is made for it under Part B of the drug definition. Part C of the drug definition, however, specifically excludes foods. This then raises the question: How is food defined for the purpose of part C? Stated another way, is it the intent of part C to exclude all substances normally defined as foods, regardless of their intended use? Reading the definition of food under subsection f is hardly helpful.

This issue was partially answered in the case of *Nutrilab, Inc., et al. v. Schweiker*, 713 F.2d 335 (7th Cir. 1983) (discussed in the case studies section of this chapter), in which the court considered whether a weight-reduction product known as a starch blocker is a food or drug. The plaintiffs argued the product was a food because it was derived from kidney beans. The court disagreed, finding for the FDA on the basis that the product neither fit the statutory definition of food nor the commonsense definition of food, in that people use food primarily for taste, aroma, or nutritive value. Most likely Congress intended to exclude foods when consumed in their ordinary manner from part C because all foods when ingested affect the structure or function of the body in some manner merely because of metabolism. Thus, unless excluded, all foods would become drugs by virtue of Part C. Congress did not likely intend to exclude foods that are not intended or consumed for their ordinary purpose.

The FDCA has created at least two special categories of foods, including “special dietary foods” and “medical foods.” Without this legal recognition, the FDA would likely regard articles falling into these categories as drugs.

**Special Dietary Foods**

Under the FDCA, special dietary foods include, but are not limited to those supplying a special dietary need that exists by reason of a physical, physiological, pathological, or other condition, including but not limited to the condition of disease, convalescence, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, or the need to control the intake of sodium. (21 U.S.C. § 411(3)(A))

Examples of products in this category include infant formulas, artificial sweeteners, and caloric supplements.
Medical Foods

Medical foods include foods formulated for oral use under the supervision of a physician and that are intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements are established by medical evaluation (21 U.S.C.A § 360ee). Examples of medical foods include foods formulated without the amino acid phenylalanine for phenylketonuria, and folic acid, B6, B12 combination products for hyperhomocysteinemia.

Nutraceuticals and Functional Foods

Some believe that the FDA should recognize additional classifications of food products called “nutraceuticals” and “functional foods.” The vague category of nutraceuticals would include foods that provide health or medical benefits, including the prevention and treatment of disease. Advocates of this product classification contend that the current system deters the development of a substantial number of beneficial food-related products, because the FDA could regard the products as drugs. Another category of product some would like distinguished by law is one called “functional foods.” These include foods that have been fortified or enhanced, often with a dietary supplement, such as drinks with ginseng or kava kava added and foods fortified with calcium. Currently the law does not recognize any category of articles as nutraceuticals or functional foods, and the FDA has not felt the need to do so.

Health Claims for Foods

In the 1980s some major food manufacturers began making various types of health claims for their products, causing considerable controversy with the FDA. One such controversy arose when studies at the time indicated that the ingestion of psyllium might lower cholesterol levels. Cereal manufacturers whose products contained fibrous psyllium thus proclaimed the value of their products in reducing cholesterol levels. The FDA believed that these claims made the products drugs and warned the cereal manufacturers. OTC drug manufacturers who produced psyllium laxatives were also concerned, but for a different reason; their products were regulated as drugs and because of this, they could not promote their products as effective for lowering cholesterol without being charged for misbranding. Thus, they felt the cereal manufacturers had an unfair advantage if the FDA allowed them to label their products with the health claim.

The FDA continued to struggle with this issue for years, as evidenced by the case of United States v. Undetermined Quantities of an Article of Drug Labeled as Exachol, 716 F. Supp. 787 (S.D.N.Y. 1989). In this case, the manufacturer of a product called Exachol distributed literature proclaiming that the product was useful in the prevention and treatment of coronary disease. As a result, the FDA brought legal action against the company, contending that the product, composed of lecithin, phosphatidyl ethanolamine, phosphatidylcholine, and several other natural products, was a drug on the basis of the therapeutic claims. The manufacturer then argued that the product was a special dietary food, not a drug. The court found that the FDA permitted some foods to be labeled with appropriate health-related messages. Thus, concluded the court, it would be inconsistent for the agency to single out Exachol as a drug while failing to take action against other such products.

This confusion over what health claims would be appropriate for food products and whether they could escape being branded as drugs by sliding into the special dietary food category prompted Congress to enact the Nutrition Labeling and Education Act of 1990 (NLEA) (P.L. 101-535) that...
amends section 403 of the FDCA. In part, the amendment for the first time allowed food labeling to contain a health or disease-prevention claim, but only if the FDA had promulgated a regulation approving the claim and establishing the conditions under which the claim can be used. The FDAMA has since modified the NLEA to permit health claims without the requirement that the FDA must issue a regulation, as long as there is “significant scientific agreement,” as determined by the FDA. Pursuant to this law, the FDA issued regulations for food products in 1993 (58 Fed. Reg. 2478, January 6, 1993; 21 C.F.R. part 101) and for dietary supplements in 1994 (59 Fed. Reg. 395, January 4, 1994; 21 C.F.R. parts 20 and 101). Under the regulations, the FDA will authorize a health claim for a food or dietary supplement only if the supplier submits a petition containing considerable information and evidence supporting the claim.

Dietary Supplements Versus Drugs

The NLEA was not popular among suppliers and consumers of dietary supplements, who feared that the law unduly empowered the FDA to restrict the dietary supplement industry. It is important to recognize that at that time, even though dietary supplements were commonly known by the public by that term and commonly marketed, the law did not recognize dietary supplements as a separate legal class of products. After intense lobbying, Congress reacted by passing the Dietary Supplement Health and Education Act of 1994 (DSHEA) (P.L. 103-417), further amending the FDCA by legally creating the category of dietary supplements and significantly altering the FDA’s authority to regulate dietary supplements. The NLEA and its regulations remain in effect to the extent that they are not specifically contradicted by DSHEA.

Essentially, DSHEA mandates that the FDA regulate dietary supplements more as a special type of food than as drugs, which had been the agency’s position under the NLEA. The FDA cannot require premarket approval of dietary supplements as they do for drugs. Thus, the manufacturer is responsible for determining if its product is safe and that its claims about the product are substantiated by adequate evidence. Moreover, except for new dietary supplements, the manufacturer does not have to provide the FDA with the evidence that it relies on to substantiate the product’s safety and efficacy. DSHEA generally prohibits the FDA from regulating dietary supplements as food additives as well, because food additives require premarket approval by the FDA, and require the agency to prove that a dietary supplement is unsafe before it can remove the product from the market. Under DSHEA, a dietary supplement is defined as a product that is intended for ingestion, is intended to supplement the diet, and contains any one or more of the following:

- A vitamin
- A mineral
- An herb or other botanical
- An amino acid
- A dietary substance for use by humans to supplement the diet by increasing the total dietary intake
- A concentrate, metabolite, constituent, extract, or combination of the previous (§ 201(ff); 21 U.S.C. § 321(ff))

Nutritional Support (Structure/Function) Statements

DSHEA allows dietary supplement suppliers to make four types of nutritional support statements without fear that the statements would cause the FDA to consider the product to be a drug. These are:
1. Statements that the product will benefit a classical nutrient deficiency disease as long as it also discloses the prevalence of the disease in the United States
2. Statements that describe the role of the dietary supplement in affecting the structure or function of the body
3. Statements that characterize the documented mechanism by which a nutrient or dietary supplement acts to maintain structure or function
4. Statements describing the general well-being from consumption of a nutrient or dietary ingredient (for example: “energizer,” “relaxant,” “muscle enhancement”)

DSHEA thus exempts dietary supplements from part C of the drug definition by permitting structure/function claims. For example, a seller could promote that its cranberry tablets increase the acidity of the urine and help to maintain a healthy urinary tract. If, however, the seller made the claim that its product prevents urinary tract infections, this assertion could make the product a drug under Part B of the drug definition. Similarly, a seller could not claim a product helps avoid diarrhea associated with antibiotic use but could state that it “helps maintain healthy intestinal flora.” In an attempt to clarify the dividing line between acceptable structure/function claims and disease claims, the FDA enacted a regulation on January 6, 2000 (65 Fed. Reg. 1000; 21 C.F.R. Part 101).

To make any of these four nutritional support statements, the seller must have substantiation that they are truthful and not misleading, and the label of the product must contain the disclaimer, “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.” Also, the manufacturer must notify the FDA within 30 days if it makes one of the permitted statements.

Health or Disease Claims

Despite the fact that DSHEA greatly restricts the FDA’s premarket authority over dietary supplements and exempts dietary supplements from Part C of the drug definition, as discussed the law does not allow manufacturers to make unapproved health (disease) claims that fall under Part B of the drug definition. DSHEA does allow manufacturers to make limited health claims for dietary substances that describe the relationship between a food substance and a disease, such as “folic acid may reduce the risk of neural tube birth defects” and “calcium may reduce the risk of osteoporosis.” In order to make these claims, however, the manufacturer must receive FDA approval for the health claim as judged by the “significant scientific agreement” standard. By 1999 the FDA had approved only about 11 health claims for foods and dietary supplements, including the claims for folic acid and calcium.

Because the FDA had approved so few health claims, frustrated dietary supplement manufacturers challenged the legality of the FDA’s premarket approval requirement for health claims and the legality of the FDA’s procedure for determining “significant scientific agreement” in a 1999 U.S. Court of Appeals decision, Pearson v. Shalala, 164 F.3d 650 (1999). In Pearson, four dietary supplement manufacturers, who had their health claims rejected by the FDA, successfully argued that requiring premarket approval of health claims violates the First Amendment, and that the FDA lacks sufficient criteria for explaining why a health claim does not meet the “significant scientific agreement” standard. The court agreed with the plaintiffs and felt that complete suppression of health claims, unless they are false or misleading, is too restrictive, when disclaimers (for example, “the evidence is inconclusive that antioxidant vitamins will reduce the risk of certain kinds of cancer”) on the label would accomplish the FDA’s objective. The court of appeals ordered the case remanded back to the district court, whose decision it reversed, with instructions that the FDA articulate clear standards.
as to what constitutes “significant scientific agreement.” The FDA declined to appeal *Pearson* to the Supreme Court.

The *Pearson* decision ultimately produced a profound change in how the FDA evaluated health claims. The agency now essentially allows two types of health claims, unqualified and qualified. Unqualified health claims are allowed if authorized by the agency pursuant to the significant scientific agreement test. Qualified health claims (pursuant to *Pearson*) may be made when the claim does not meet the significant scientific agreement test and the claim would be misleading without the qualification. Qualified claims will be allowed when there is more evidence for the claim than against it. (See 65 Fed. Reg. 59,855 (Oct. 6, 2000).) The qualified claim must be truthful and not misleading and appropriately indicate the level of scientific support; for example, “Scientific evidence suggests but does not prove” or “Some evidence shows the nutrient may be beneficial but there is insignificant scientific evidence to prove the effect.” The agency continues to aggressively police manufacturers who make unapproved health claims that it regards as false or misleading.

**Dietary Supplements Containing Drugs**

On occasion a dietary supplement may contain a drug, raising the issue of whether the product is actually a drug and not a dietary supplement. The FDCA excludes from the definition of dietary supplement any article that was approved as a new drug, unless prior to the approval it was marketed as a dietary supplement or food (21 U.S.C. §321(ff)(3)(B)). In the case of *Pharmanex, Inc. v. Shalala*, 35 F. Supp. 1341 (2001 WL 741419 (D.Utah)), Pharmanex challenged the FDA’s decision that its product, Cholestin, which contained red yeast rice, was a drug and not a dietary supplement. Traditional red yeast rice has been eaten by the Chinese for centuries and is regarded by the Chinese as a health food. On this basis, the manufacturer argued Cholestin is a dietary supplement. The court, however, agreed with the FDA’s determination. The FDA established that Cholestin contained significant amounts of lovastatin, a cholesterol-lowering drug approved by the FDA in 1987. The FDA further proved that Pharmanex carefully manufactured the production of Cholestin to contain high levels of lovastatin not found in traditional red yeast rice. In effect, the agency proved the company was marketing lovastatin, not traditional red yeast rice. Pharmanex retorted that, nonetheless, lovastatin was present in some foods marketed in the U.S. long before it was approved by the FDA, and therefore it must be considered a dietary supplement. The court, however, agreed with the FDA’s interpretation that traditional red yeast rice does not contain lovastatin, and that lovastatin itself was not marketed as a dietary supplement, food, or food component prior to 1987.

**Safety Issues and Ephedra Products**

Because dietary supplements are regulated much as foods rather than drugs, the FDA can only remove a dietary supplement from the market on the basis of public safety if the agency can prove the product is adulterated (21 U.S.C. § 331(a), (b), (c), (k)). DSHEA provides that a dietary supplement is adulterated if it presents a “significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labeling; and, if no conditions of use are recommended or suggested, then under ordinary conditions of use” (21 U.S.C. §342(f)(1)).

Pursuant to its application and interpretation of the law, the FDA issued a final regulation in 2004 banning all ephedrine alkaloid dietary supplement (EDS) products (69 Fed. Reg. 6788 (Feb. 11, 2004)). (Note: Ephedrine alkaloids [ephedra] is an extract of the ma huang plant and has been used as a natural medicinal agent in China for centuries. It should be distinguished from OTC drug products with structurally related active ingredients.) This final regulation was the culmination of a long investigative process beginning in the early 1990s when the FDA began receiving adverse event reports suggesting injury and illness associated with the use of EDS products. The administrative
record reflecting the regulatory process contains over 133,000 pages of scientific data, expert reviews, comments, and other materials. In addition, the FDA commissioned expert reviews of the scientific evidence and assessed the findings of these expert reviews. After all this review, the FDA concluded that although EDS is promoted to achieve weight loss, enhance athletic performance, and increase energy, its effects are temporary, modest, and generally do not improve health. In contrast, the agency found that EDS increases the risk of serious adverse events including heart attacks, strokes, and death.

The passage of the regulation was hastened after highly publicized accounts that EDS use led to the death of some high-profile athletes, such as Korey Stringer of the Minnesota Vikings and Steve Bechler of the Baltimore Orioles. Accounts such as these prompted Congress to issue a resolution that the FDA should immediately remove EDS from the market. Shortly after the enactment of the regulation, however, an EDS manufacturer sued the FDA in federal court in Utah contending that the regulation was invalid (Nutraceutical Corp. v. Crawford, 364 F.Supp.2d 1310 (April 12, 2005)). The court ruled for the plaintiff and invalidated the regulation on the basis that the FDA improperly applied a risk-benefit analysis and failed to provide sufficient evidence that EDS poses a significant risk in the dose recommended by the plaintiff. The FDA appealed, resulting in the court of appeals finding for the FDA, reversing the district court’s decision and reinstating the regulation banning EDS products (Nutraceutical Corp. v. Von Eschenbach, 459 F.3d 1033 (10th Cir. 2006)).

Criticisms of DSHEA
DSHEA has proved thus far to be an extremely controversial law. Critics have three major concerns about DSHEA. First, they fear that the law allows the marketing of unsafe dietary supplements and contend that it prevents the FDA from acting aggressively enough to protect the public. Second, critics are concerned over a lack of consumer information about the dangers of taking many dietary supplements with certain OTC and prescription medications. Most dietary supplement labeling does not warn users of these potential adverse effects. Third, critics argue that dietary supplement labeling standards lack quality standards for strength and purity because manufacturers are not required to register themselves or their products with the FDA prior to marketing them, and no manufacturing standards exist for dietary supplements. Quality assays of some dietary supplements have showed that strengths vary from those on the label and even vary from pill to pill in the same bottle. Some products were found not to contain the active ingredient, and some contained ingredients other than those stated on the label.

In response to these concerns over quality standards, the FDA proposed regulations in 2003 requiring that dietary supplement manufacturers comply with current good manufacturing practices (CGMP) in such a manner that the products will not be adulterated or misbranded. The regulations also require manufacturers to evaluate the identity, purity, quality, strength, and composition of their products (68 Fed. Reg. 12158 (March 13, 2003)). The regulations were scheduled for final action in December 2006.

Implications of DSHEA for Pharmacists
In light of the decreased government regulation over dietary supplements since DSHEA, pharmacists have an important role in providing accurate product information to patients and assisting them with product selection. If possible, pharmacists should steer patients to products conforming to United States Pharmacopeia (USP) or National Formulary (NF) standards, or at least products in which manufacturers can attest to quality and uniformity standards.

Pharmacists should not promote dietary supplements on the basis of unapproved health or disease claims, because this could violate the FDCA. However, pharmacists should not hesitate to
counsel, educate, and provide advice to patients about the use of a supplement product for a disease, especially when asked by the patient. DSHEA permits pharmacists to display certain publications, such as articles, book chapters, books, and abstracts of peer-reviewed scientific publications, used in conjunction with the sale of dietary supplements. To conform to the law, however, these publications must be reprinted in their entirety; must not be false or misleading; must be presented with other publications, if available, about the product so as to present a balanced view; must be physically separate from the actual product; and must not have appended to them any information by sticker or other method.

Drugs Versus Devices

Before the passage of the Medical Device Amendment (MDA) of 1976, the FDA lacked the authority to approve devices for safety and efficacy prior to their commercial distribution. This inadequacy forced the FDA to declare that certain devices were drugs, which often resulted in litigation. For example, in United States v. Article of Drug Bacto Unidisk, 394 U.S. 784 (1969), the FDA successfully established that antibiotic sensitivity disks fall under the drug definition. In another case, United States v. Article of Drug Ova II, 414 F. Supp. 660 (D.N.J. 1975), the FDA failed to prove that a home pregnancy testing kit is a drug. The court determined that because pregnancy is not a disease, the kit is not a diagnostic test for a disease. The MDA differentiates devices from drugs by stating that a device does not achieve any of its principal intended purposes through chemical action and is not dependent on being metabolized for the achievement of any of its principal intended purposes. The term device does include in vitro diagnostic products used to aid in the diagnosis of disease or verification of pregnancy.

When a device is used in conjunction with a drug, the legal distinction becomes less clear. The FDA has stated that many factors may determine whether a product is a device or a drug.

- Is the product intended to deliver drugs to the patient, but is not prefilled by the manufacturer (e.g., an empty implantable infusion pump)?
- Is the drug component included solely to make the product safer (e.g., a surgical drape impregnated with antimicrobial agents)?
- Is the drug component intended to have a therapeutic effect (e.g., an intrauterine contraceptive device that releases a hormone)?

The manufacturer of a drug delivery device must establish that the device and the drug will not have deleterious effects on one another. Although problems of classification still occur, the 1976 device amendment has greatly clarified the distinction between drugs and devices, and has given the FDA significantly more enforcement authority over devices. The MDA’s comprehensive device classification system is discussed later in this chapter.

Drugs Versus Cosmetics

A cosmetic may become a drug if its manufacturer promotes it for a therapeutic purpose, despite the product chemistry. In United States v. An Article . . . Consisting of 216 Cartoned Bottles, More or Less, “Sudden Change,” 409 F.2d 734 (2nd Cir. 1969), the manufacturer distributed a lotion composed of bovine albumin and distilled water. When applied to the skin and allowed to dry, the lotion left a film that tightened the skin, thus temporarily masking imperfections and making the skin look smoother. The manufacturer’s advertisements claimed that the lotion would “lift out puffs” or give a “facelift without surgery.” The court refused to apply to these claims the standard of what a reasonable consumer would believe, but rather applied the standard of what an “ignorant, unthinking, and credu-
lous” consumer would believe. On the basis of this standard and the manufacturer’s claims, the court
found that the lotion was a drug but would cease to be a drug once the claims were discontinued.

On the other hand, in United States v. An Article of Drugs . . . 47 Shipping Cartons, More or Less,
“Helene Curtis Magic Secret,” 331 F. Supp. 912 (D. Md. 1971), the court concluded that such claims
as being a “pure protein” and causing an “astringent sensation” would not persuade even ignorant,
unthinking, and credulous consumers that the product would alter their appearance. Therefore,
this product was not held to be a drug.

Labels and Labeling

The FDCA differentiates the definition of label from that of labeling:

(k) The term “label” means a display of written, printed, or graphic matter upon the immediate container of
any article; and a requirement made by or under authority of this Act that any word, statement, or other in-
formation appearing on the label shall not be considered to be complied with unless such word, statement,
or other information also appears on the outside container or wrapper, if any there be, of the retail package
of such article, or is easily legible through the outside container or wrapper. (§ 201(k); 21 U.S.C. § 321(k))

(m) The term “labeling” means all labels and other written, printed, or graphic matter (1) upon any article
or any of its containers or wrappers, or (2) accompanying such article. (§ 201(m); 21 U.S.C. § 321(m))

The term label, as the definition indicates, refers to information required on the container or
wrapper. The term labeling has a far broader application. Although the term labeling includes the
label, it also applies to the information “accompanying” the drug, such as the package insert. The
legal interpretation of the word accompanying can be important in establishing whether misbrand-
ing has occurred. If the literature is deemed to accompany the product, it is labeling. If it is deemed
not to accompany the product, it is advertising. The line between labeling and advertising is not al-
tways a clear one, leading to controversies.

In United States v. Guardian Chemical Corporation, 410 F.2d 157 (2nd Cir. 1969), the manufacturer
discovered that its product, sold for the purpose of cleansing dairy apparatus, also was effective in
treating kidney and bladder stones. Ultimately, the company prepared and distributed brochures
to the medical profession to promote the product, now named Renacidin, for these purposes. The
FDA contended that Renacidin was a drug and that the bottles and the brochures were misbranded
because they did not contain the label and labeling information required by law. The court agreed
with the FDA, holding that printed pamphlets or brochures need not be shipped with the article to
constitute labeling. They may be sent either before or after the article and still “accompany” it, as
long as the distribution of the drug and the brochures are part of an “integrated distribution pro-
gram” to sell the product.

In general, courts have held that information is labeling if the written materials are part of an
integrated distribution program, have a common origin and destination, and explain the drug. The
distinction between labeling and advertising for prescription drugs may not be that important today
because each is subject to regulation by the FDA and must contain all of the information approved
by the FDA, as discussed later in this chapter.

Official Compendia

Part A of the drug definition recognizes particular compendia as legal sources of drug standards. One
of these compendia, the USP, is published by the United States Pharmacopeial Convention (USPC), an
independent, private organization jointly founded in 1820 by physicians and pharmacists of the
time, who were concerned that various medicinal ingredients and preparations under the same
names differed considerably in potency, quality, and composition. To set uniform standards for these products, the USPC elected scientific experts to publish the USP. It has continued to establish standards ever since.

Although the USPC is a private organization, independent of the FDA, the FDA actively participates in the development and modification of the standards contained in the USP’s monographs, which establish the approved titles, definitions, descriptions, and standards for identity, quality, strength, purity, packaging, stability, and labeling for a drug. The USPC publishes the monographs of many of the drugs marketed in the United States.

Before 1980, the USP contained monographs of active ingredients, and the NF contained monographs of inactive ingredients. In 1980, the two books were combined into one compendium, commonly referred to as the USP/NF, which now serves as the official compendium for drug standards in the United States.

The other official compendium stated under the FDCA is the Homeopathic Pharmacopoeia of the United States (HPUS), which has been in continuous publication since 1897. The HPUS defines homeopathy as the “art and science of healing the sick by using substances capable of causing the same symptoms, syndromes and conditions when administered to healthy people.” The standards for the homeopathy products contained in the HPUS are established by the Homeopathic Pharmacopoeia Convention of the United States (HPCUS). This is a private, nonprofit organization of scientific experts in homeopathy. Because of the recent resurgence of homeopathy and a resultant need for continuous updates, HPCUS has republished the HPUS since 1988 as the HPUS Revision Service, a loose-leaf binder publication that allows for continual revisions without the need to reprint an entirely new volume.

Under the FDCA, a drug recognized in the USP/NF or HPUS must meet all compendium standards or it will be considered misbranded or adulterated. Similarly, a drug is considered misbranded or adulterated if it is not recognized in the USP/NF or HPUS, yet purports to be so recognized.

### Study Scenarios and Questions

1. A company manufactures and markets capsules filled with pulverized sheep bone. It promotes the product as a treatment for anemia and various blood disorders. Explain whether this product is a drug or a dietary supplement.

2. Assume for question 1 that the company promoted the product with the claim that it “restores healthy blood” instead. Explain whether this would change your answer to question 1.

Questions 3 through 7 relate to the following hypothetical situation:

Sue is a pharmacist who loves to travel internationally, studying the use of natural products in other societies and cultures. On one of her trips to a rain forest in Africa she noticed that a few natives of one of the tribes chewed a certain wild root known as acumana to help them sleep. She chewed the root and indeed felt it helped her sleep. While investigating this root she was surprised to find that although the root was not uncommon, its medicinal effects, if any, were scarcely mentioned in any literature. Sue brought the root back to the United States and found it grew readily under greenhouse conditions. Sue formed a company that produced and bottled tablets made from the dehydrated and pulverized root. She heavily marketed the product, which she labeled with the name Acuxen, across the country as an “aid in relaxation and sleep.” The FDA is investigating Sue’s company to determine if she is marketing a drug or dietary supplement.
3. Based on the facts in this case, is Acuxen most likely a food, drug, or dietary supplement, and why? (To answer this question you must consider both the composition of Acuxen and the indication.)

4. If Sue made the root product as a topical patch, why might your answer be different than the one above?

5. Assuming that the product in question 3 is a dietary supplement based on composition and it is a structure/function claim, on what legal basis could the FDA still challenge the product?

6. Explain why your answer in question 3 might change if Sue labeled Acuxen for use in insomnia? Assuming this is a health or disease claim, would it matter whether the claim was made on the label or in pamphlets attached to the product?

7. Assume that, before purchasing Acuxen, a patient in a pharmacy asked the pharmacist about the product and that the pharmacist remarked that in his opinion the product seemed to be effective for insomnia and also in preventing some types of dementia. Has the pharmacist violated the FDCA?

8. The Exachol decision was issued prior to DSHEA. How might the decision be different today?

9. Differentiate between the disclaimer required for a structure/function claim on a dietary supplement product label and a health claim pursuant to the Pearson decision.

Prohibited Acts, Penalties, and Enforcement

Prohibited Acts: The Law

Section 301 of the FDCA in part prohibits the following acts:

- (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.
- (b) The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce.
- (c) The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.
- (d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 404 or 505.
- (e) The refusal to permit access to or copying of any record as required . . . or the failure to establish or maintain any record, or make any report, required . . . or the refusal to permit access to or verification or copying of any such required record.
- (f) The refusal to permit entry or inspection as authorized by section 704.
- (g) The manufacture within any Territory of any food, drug, device, or cosmetic that is adulterated or misbranded.
- (i)(3) The doing of any act which causes a drug to be a counterfeit drug, or the sale or dispensing, or the holding for sale or dispensing, of a counterfeit drug.
The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.

The introduction or delivery for introduction into interstate commerce of a dietary supplement that is unsafe under section 413 of this title. (§ 301; 21 U.S.C. § 331)

Section 303(a)(1) then provides that any violator of section 301 shall be imprisoned for not more than 1 year, fined not more than $1,000, or both. Under section 301(a)(2), if the violator commits a second offense of the act or commits a violation with the intent to defraud or mislead, the violator could be imprisoned for up to 3 years and/or fined up to $10,000. (See United States v. Hiland in the case studies section of this chapter.) Section 303 also singles out several violations that warrant much more severe penalties, such as violations of the Prescription Drug Marketing Act discussed in Chapter 3.

**Explanation of the Law**

The FDCA establishes two major offenses—adulteration and misbranding—which are explained later in this chapter. Nearly every violation of the FDCA constitutes one or both of these offenses. The violations are of a strict liability nature. In other words, the commission of any of the listed offenses violates the FDCA, regardless of the person’s intentions or knowledge. Under section 301(c), for example, a pharmacist who unknowingly and innocently receives an adulterated or misbranded drug and subsequently sells it to a consumer has violated the act. Section 303(c) of the act, however, provides that a pharmacist who sells the drug in good faith will not be subject to any penalties if on request the pharmacist furnishes the FDA with information about the source of supply.

Although section 301 is mostly self-explanatory, certain sections warrant more attention by pharmacists. Section 301(i)(3) makes it illegal for a pharmacist to make, dispense, or hold for dispensing a counterfeit drug. The definition of counterfeit drug in section 201(g) suggests that a pharmacist may violate section 301(i)(3) if the pharmacist dispenses a placebo or dispenses a particular drug and labels it as another drug.

Pharmacists who repackage or relabel drugs, either prescription or OTC drugs, must pay particular attention to section 301(k). If the new label does not conform to FDA specifications in all particulars, the pharmacist may be charged with misbranding. Pharmacists should ensure that the label of the repackaged drug contains the identical information that the manufacturer’s label contains.

**Enforcement**

The FDA has the authority to enforce the FDCA in several ways. Under section 302, the FDA can bring an injunctive action against the violator to cause it to cease its illegal activity. Under section 303, the FDA can institute criminal proceedings against violators, resulting in fines, imprisonment, or both. Section 304 allows the FDA to seize any adulterated or misbranded food, drug, or cosmetic in interstate commerce. Because of the strict liability nature of section 302 and the realization that minor violations of the act should not be subject to criminal prosecution or seizure actions, Congress added section 309, which allows the FDA to send a warning letter to the violator as a first step when such an action would adequately serve the public interest.

**Corporate Officer Liability**

The U.S. Supreme Court has held that corporate officers can be convicted when other corporate employees violate the FDCA. In United States v. Dotterweich, 320 U.S. 277 (1943), the president of a repack-
aging and relabeling company was convicted of adulteration and misbranding even though there was no evidence that he knew of the wrongful acts. The Court’s rationale was that it is better to place the burden on those in a position to discover the violations than on an innocent and helpless public.

In United States v. Park, 421 U.S. 658 (1975), the president of a nationwide grocery chain was charged with holding food products under unsanitary conditions. He contended that he delegated the responsibility for sanitation to employees and could not be expected to oversee all corporate operations personally. The Court acknowledged that a defendant’s “powerlessness” to prevent or correct the violation may be raised as a defense, but the burden falls on the defendant to prove this. Finding the defendant liable under the FDCA, the Court stated that the act imposes a duty not only to seek out and correct violations, but also to implement procedures to ensure that violations will not occur. This requirement on corporate officers may be demanding and onerous, stated the Court, but no more so than the public has a right to expect in light of the effect on the public health and well-being.

Product Recalls

One method of removing adulterated or misbranded products in interstate commerce is by means of recall. The FDA does not have the statutory authority to order a product recall, but may ask a company to recall a product as an alternative to injunctive action or seizure. Alternately, a manufacturer may initiate a product recall without FDA involvement. In either event, the FDA does have the authority to prescribe the procedures to which the recall must conform.

Drug recalls are divided into three classes.

1. Class I recalls are issued when there is a reasonable probability that the product will cause serious, adverse health consequences or death.
2. Class II recalls occur when the product may cause temporary or medically reversible adverse health consequences, but the probability of serious adverse consequences is remote.
3. Class III recalls apply to products that are not likely to cause adverse health consequences.

The manufacturer is responsible for notifying sellers of the recall. In turn, sellers are responsible for contacting consumers, if necessary. Manufacturer recall notices may be delivered by means of letter, telegram, telephone, sales representatives, and so forth. Guidelines issued by the FDA require that written notices for class I, class II, and some class III recalls be sent by first-class mail with the envelope and letterhead conspicuously marked, preferably in red, URGENT: DRUG RECALL. Many pharmacy publications also provide current lists of recalled products.

A pharmacist is responsible for knowing which drug products have been recalled. Furnishing a recalled product may violate the FDCA because the product is likely adulterated or misbranded, and a pharmacist might have difficulty asserting a good-faith defense. The pharmacist might also be subject to civil liability in the event of patient injury.

Adulteration

Adulteration: The Law

Section 501 of the FDCA in part provides that a drug or device shall be deemed to be adulterated:

(a)(1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or (2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or (B) if it is a drug and the methods used in, or the
facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice . . .; or (3) if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health; or (4) if (A) it bears or contains, for purposes of coloring only, a color additive which is unsafe . . .

(b) If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium. ***No drug defined in an official compendium shall be deemed to be adulterated under this paragraph because it differs from the standard of strength, quality, or purity therefore set forth in such compendium, if its difference in strength, quality, or purity from such standards is plainly stated on its label.***

(c) If it is not subject to the provisions of paragraph (b) of this section and its strength differs from, or its purity or quality falls below, that which it purports or is represented to possess.

(d) If it is a drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength or (2) substituted wholly or in part therefore. (§ 501; 21 U.S.C. § 351)

Explanation of Adulteration

Most of the adulteration provisions apply to manufacturers. A pharmacy may be deemed a manufacturer if it repackages or compounds medications for sale under certain conditions, however, as discussed in the compounding section of Chapter 3.

A drug may be adulterated under the act, even if it is pure, because a drug is deemed adulterated if it is

• Prepared, packed, or held in conditions where it may have been contaminated
• Exposed to a container that may have contaminated it
• Manufactured under conditions that do not conform to current GMP

These provisions in the law are intended to regulate the facility and the means of production rather than the product itself. There are two reasons for this approach. First, it is much easier for the FDA to inspect a relatively few manufacturing plants than the thousands of drug products that these plants produce. Second, the health and safety risk to the public is much lower if the FDA can prevent adulteration rather than wait and remove an adulterated product from the market.

The law also provides that a drug is adulterated if it contains an unsafe color additive. Moreover, a drug that is subject to compendia standards is deemed adulterated if its strength, quality, or purity differs from those standards, unless the variations are stated on the label. If the drug is not subject to compendia standards, it is deemed adulterated if its strength, quality, or purity differs from those stated on the label. On the basis of this provision, a drug could be simultaneously adulterated and misbranded.

Current Good Manufacturing Practice (CGMP)

Section 501(a)(2)(B) specifically declares that a drug is adulterated unless it is manufactured in accordance with “current good manufacturing practice.” CGMP is a set of regulations that establishes minimum requirements for the methods, facilities, or controls used in the manufacture, processing, packaging, or holding of a drug product (21 C.F.R. §§ 211.1–211.208). The intent of the CGMP regulations is to ensure that the drug is safe and meets the quality and purity requirements. The CGMP applies to manufacturers, not pharmacies, unless the pharmacies engage in activities in which they may be deemed manufacturers.
Manufacturers must be registered with the FDA and are normally inspected by the FDA for compliance with CGMP once every 2 years. The inspections are designed to

- Confirm that the production and control procedures result in the proper identity, strength, quality, and purity of the drugs
- Identify deficiencies
- Ensure correction of the deficiencies

Noncompliance with the CGMP could result in litigation against the company and a declaration that the drugs are adulterated. Drugs under the CGMP are selected for analysis on the basis of their medical importance, market share, number of similar products in the marketplace, and the previous compliance record of their manufacturer. The FDA looks for various defects, such as sub-potency, particulates, lack of content uniformity, and dissolution failures. When unacceptable deviations are substantiated by further testing, the manufacturer is asked to investigate the problem and, if necessary, recall the drug voluntarily. If the manufacturer does not correct the problem, the FDA may seize the product.

Product Tampering

In response to the intentional contamination of Tylenol capsules on retailers’ shelves in 1982, Congress passed the Federal Anti-Tampering Act (18 U.S.C. § 1365), making it a federal offense to tamper with consumer products. Tampering is defined in the act as improper interference with the product for the purpose of making objectionable or unauthorized changes. The act gave regulatory authority to the Federal Bureau of Investigation, the U.S. Department of Agriculture, and the FDA.

The FDA promulgated regulations in 1982 (21 C.F.R. § 211.132) requiring that certain OTC drugs, cosmetics, and devices be manufactured in tamper-resistant packaging. Violation of this regulation may be deemed adulteration, misbranding, or both. A tamper-resistant package is defined as “one having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred.” The regulations require tamper-resistant packaging, not tamper-proof packaging, because technology does not exist to eliminate the risk of tampering completely.

Misbranding

Misbranding: The Law

Section 502 of the FDCA provides that a drug or device shall be deemed to be misbranded

(a) If its labeling is false or misleading in any particular. Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved...for such drug and is based on competent and reliable scientific evidence. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request. In this paragraph, the term “health care economic information” means any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention.
(b) If in a package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count.

c) If any word, statement, or other information required is not prominently placed on the label, with such conspicuousness and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

(e)(1)(A) If it is a drug, unless its label bears, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula) (i) the established name (as defined in subparagraph (3)) of the drug, if there is such a name; (ii) the established name and quantity or, if determined to be appropriate by the Secretary, the proportion of each active ingredient, including the quantity, kind, and proportion of any alcohol, and also including whether active or not the established name and quantity or if determined to be appropriate by the Secretary, the proportion of any bromides, ether, chloroform, acetanilide, acetophenetidin, amidopyrine, antipyrine, atropine, hyoscine, hyoscyamine, arsenic, digitalis, digitalis glucosides, mercury, ouabain, strophanthin, strychnine, thyroid, or any derivative or preparation of any such substances, contained therein, except that the requirement for stating the quantity of the active ingredients, other than the quantity of those specifically named in this subclause, shall not apply to nonprescription drugs not intended for human use; and (iii) the established name of each inactive ingredient listed in alphabetical order on the outside container of the retail package and, if determined to be appropriate by the Secretary, on the immediate container, as prescribed in regulation promulgated by the Secretary, except that nothing in this subclause shall be deemed to require that any trade secret be divulged, and except that the requirements of this subclause with respect to alphabetical order shall apply only to nonprescription drugs that are not also cosmetics and that this subclause shall not apply to nonprescription drugs not intended for human use.

(3) As used in paragraph (1) the term “established name” means (A) the applicable official name, or (B) if there is no such name and the drug is an article recognized in an official compendium, then the official title in the compendium or (C) if neither clause (A) nor clause (B) of this paragraph applies, then the common or usual name.

(f) Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement.

(g) If it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein.

(h) If it has been found to be a drug liable to deterioration, unless it is packaged in such form and manner, and its label bears a statement of such precautions.

(i)(1) If it is a drug and its container is so made, formed, or filled as to be misleading; or (2) if it is an imitation of another drug; or (3) if it is offered for sale under the name of another drug.

(j) If it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling, thereof.

(m) If it is a color additive the intended use of which is for the purpose of coloring only, unless its packaging and labeling are in conformity with applicable packaging and labeling requirements.
(n) Unless the manufacturer, packer or distributor includes in all advertisements and other descriptive printed matter a true statement of (1) the established name printed prominently and in type at least half as large as that used for any trade or brand name, (2) the formula showing quantitatively each ingredient of the drug and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness.

(p) If it is a drug and its packaging or labeling is in violation of an applicable regulation of the Poison Prevention Packaging Act of 1970. (§ 502; 21 U.S.C. § 352)

As noted previously, failure to manufacture certain OTC products in a tamper-resistant package is also misbranding.

**Explanation of Misbranding**

Whereas adulteration deals with a drug’s strength, purity, and quality, misbranding focuses on representations made by the manufacturer on the label or labeling. The FDA must approve, as part of the premarket approval process, the exact wording of a drug’s label and labeling. The agency has often used the misbranding provisions of the act to prevent manufacturers from marketing products in violation of the law.

**False or Misleading Labeling**

That a label shall not be false or misleading under section 502(a) is self-explanatory. The FDAMA added the provision regarding health care economic information. Before the FDAMA, the subject of drug manufacturers supplying pharmacoeconomic information to health care decision makers had been controversial. Because the FDA does not approve pharmacoeconomic data as part of the drug’s labeling, the question was whether a manufacturer that provided this information would be guilty of misbranding. Now, under the law, health care economic information provided to formulary decision makers is permissible as long as the information is accurate and reliable.

**Habit-Forming Drugs**

Before the FDAMA, section 502 contained a provision stating that the labeling of any drug containing a substance found to be habit-forming must contain a warning to this effect. The FDAMA deleted this provision, thus making whether to include the warning discretionary with the manufacturer. Manufacturers are still required to adequately describe the habit-forming characteristics of the drug in the “Drug Abuse and Dependence” section of the package insert.

**Established Names of Drugs**

Section 502(e) obviously contains a significant amount of information. The important points to note from this section are that the law requires the listing of any active ingredient for both prescription and nonprescription drugs and the quantity of each active ingredient (unless the nonprescription drug is not for human use). Section 502(e) also requires that in most situations the labeling contain a list of the established name of each inactive ingredient in alphabetical order for both prescription drugs and nonprescription drugs (unless the nonprescription drug is also a cosmetic or not for human use). Before the FDAMA, the listing of inactive ingredients was not required.

**Adequate Directions for Use**

Section 502(f) states that the labeling must contain “adequate directions for use,” and “adequate warnings against use” by children and others for whom use may be dangerous. “Adequate directions for use” in the regulations means “directions under which the layperson can use a drug safely and for the purposes for which it is intended” (21 C.F.R. § 201.5). The regulation continues by stating
that the directions for use may be deemed inadequate unless the labeling contains statements of all conditions, purposes, or uses for which the drug is intended and for which the drug is commonly used. As the court held in *Alberty Food Products Co. v. United States*, 185 F.2d 321 (9th Cir. 1950), merely stating the proper way to take a drug is not adequate. The labeling must be complete enough to inform the consumer that the drug should be used for the consumer’s particular ailment.

In addition to the statements of all conditions, purposes, or uses, “adequate” labeling of a drug must include

- The quantity or dosage for each intended use and for persons of different ages and physical conditions
- The frequency of administration or application
- The duration of administration or application
- The time of administration or application (in relation to meals, onset of symptoms, or other factors)
- The route or method of administration or application
- The preparation necessary for use (e.g., shaking, dilution)

**Adequate Information for Use**

Some drugs cannot be labeled adequately to protect the consumer and meet the “adequate directions for use” requirement of section 502(f). The FDA classifies these drugs as prescription drugs, which makes them exempt from the requirements of section 502(f). Prescription drugs must contain “adequate information for use” rather than adequate directions for use (21 C.F.R. § 201.100(c)(1)). Thus, the labeling must include such information as

- The drug’s indications
- Side effects
- Dosages
- Routes, methods, frequency, and duration of administration
- Contraindications
- Other warnings and precautions that enable a practitioner to administer, prescribe, or dispense the drug safely

Prescription drug labeling is directed to the practitioner, not the patient. Nonetheless, the FDA has increasingly been concerned that patients receive understandable information about their prescription drug medication, as evidenced by the Medication Guide program discussed in Chapter 3.

**Imitation Drugs**

Section 502(i)(2) of the FDCA provides that it is misbranding if a drug is an imitation of another drug. The FDA has invoked this section against drugs sold as imitations of controlled substances. In *United States v. Articles of Drug (Midwest Pharmaceuticals)*, 825 F.2d 1238 (8th Cir. 1987), for example, Midwest distributed and promoted a drug containing caffeine, ephedrine, and phenylpropanolamine. Advertisements for the drug contained pictures of capsules and tablets that looked exactly like various well-known amphetamine-type controlled substances. The advertisements contained no information about the drug’s ingredients, but they described the drug using various street names, such as 20/20, White Mole, and Mini-White. Finding for the FDA, the court held that a product is an imitation if it is
• Identical in shape, size, and color
• Similar or virtually identical in gross appearance
• Similar in effect to controlled substances

**Batch Certification**

Before the FDAMA, section 502 had required batch certifications for insulin and antibiotics. Early insulin preparation techniques were often crude, resulting in problems of product purity and potency. Similarly, early antibiotic preparations relied on fermentation, extraction, and purification techniques that at the time were inconsistent, resulting in variability of stability and potency. Therefore, Congress gave the FDA the authority to require that batches of insulin and antibiotics be certified by the agency before their marketing. Because antibiotics and insulin products today no longer exhibit the problems they presented in earlier years, the FDA no longer has the statutory authority to require batch certification for either insulin or antibiotics.

**Nonprescription Drug Labeling**

Nonprescription drugs, or OTC drugs, are those that are safe and effective for self-medication by consumers. Pursuant to regulations finalized in 1999 with the intent to make OTC drug labeling more “user friendly,” the label of a nonprescription drug must contain in part the following information (see 64 Fed. Reg. 13254; 21 C.F.R. Part 201 Subparts A & C):

- A statement of the identity of the product, including the established name of the drug, if any, followed by an accurate statement of the general pharmacological category of the drug or principal intended action(s) (e.g., Suphedrin, pseudoephedrine hydrochloride, nasal decongestant)
- The name and address of the manufacturer, packer, or distributor
- The net quantity of the contents of the package
- Cautions and warnings needed to protect the consumer
- Adequate directions for use (as discussed previously)
- A “Drug Facts” panel containing the following information in the following order (21 C.F.R. § 201.66):
  - Active ingredient(s) (including dosage unit and quantity per dosage unit)
  - Purpose (general pharmacological category or principal intended action)
  - Use(s) (indications)
  - Warnings (including the following subheadings in bold type)
    - “For external use only” (for topical products) or “For rectal (or vaginal) use only” for products intended for these uses
    - Do not use (listing of all contraindications)
    - Ask a doctor before use if you have (listing of all conditions and situations when the product should not be used)
    - Ask a doctor or pharmacist before use if you are (listing of all drug-drug and drug-food interactions)
    - When using this product (listing of possible side effects and substances or activities to avoid)
    - Stop use and ask a doctor if (listing of signs of toxicity and other reactions requiring immediate discontinuation)
Regulations (21 C.F.R. § 201.5) further require adequate directions for use to contain:

- The normal dose for each intended use and the doses for individuals of different ages and different physical conditions
- The frequency and duration of administration or application
- The administration or application in relation to meals, onset of symptoms, or other time factors
- The route or method of administration or application
- Any required preparation for use

The regulations provide that OTC drug labels must be easy to read and easy to understand, as well as be of a minimum size type. These format requirements are designed to make it easier for consumers to select the appropriate product and help them use the product more effectively.

Pharmacists who repackage or relabel OTC drugs for resale must comply with the same labeling requirements as manufacturers.

Professional OTC Labeling

For some OTC drug products, manufacturers publish additional labeling specifically for the health care professional, not the consumer. Called “professional labeling,” it is intended to provide information for conditions not appropriate for lay diagnosis or treatment. The FDA does not allow this information on the labeling of the marketed OTC product because it does not contain “adequate directions for use.” The concept of professional labeling arose in 1973 when panels of experts reviewing OTC drugs for safety and efficacy recommended additional labeling for such situations as pediatric dosing and the use of antacids for ulcer therapy. For example, the allowed OTC labeling indications for antacids include “heartburn,” “sour stomach,” “acid indigestion,” and so forth. The professional labeling includes indications for “the symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis . . .” (21 C.F.R. part 331).

The FDA’s position is that the information contained in professional labeling can be safely used only under the supervision of the licensed prescriber. Therefore, a pharmacist should not provide a patient with professional information even if the manufacturer has mailed this information to the pharmacist, unless the patient requests it. Of course, the pharmacist may provide the labeling to the prescriber. Although a pharmacist may recommend an OTC drug to a patient for a condition or a dosage not listed on the label, doing so may increase the pharmacist’s risk of civil liability in the event of patient injury.

Drugs That Are Both OTC and Prescription

The issue of adequate directions for use labeling also explains why some drugs are both OTC and prescription. With these drugs, the FDA has made the determination that the drug can be labeled with adequate directions for use for some indications but not others. For example, meclizine is sold OTC
for the indications of nausea, vomiting, and dizziness associated with motion sickness. The drug is sold prescription with the added indication of being possibly effective for vertigo associated with diseases affecting the vestibular system. It also explains why some drugs, such as ibuprofen, are OTC at one strength and prescription at other strengths. The 200-mg OTC ibuprofen carries the indication for mild to moderate pain, whereas the higher strengths prescription ibuprofen add indications of rheumatoid arthritis and osteoarthritis. (Chapter 3 will discuss how a drug can also be both OTC and prescription depending upon how it is switched from prescription to OTC status.)

Prescription Drug Labels and Labeling
As noted earlier, prescription drugs are labeled for the health care professional, not the patient. (Chapter 3 will discuss governmental efforts directed at labeling for the patient.)

The Commercial Container Label
The applicable regulations are somewhat detailed and, in general, require the following information on the commercial label (21 C.F.R. §§ 201.1, 201.55 and 201.100):

- The name and address of the manufacturer, packer, or distributor
- The established name of the drug product
- Ingredient information, including the quantity and proportion of each active ingredient
- Names of inactive ingredients (with certain exceptions) if not for oral use
- A statement of identity (generic and proprietary names)
- The quantity in terms of weight or measure (e.g., 100 mg)
- The net quantity of the container (e.g., 100 tablets)
- A statement of the recommended or usual dosage or reference to the package insert
- The symbol “Rx Only” or the legend: “Caution: Federal law prohibits dispensing without prescription.”
- The route of administration, if it is not for oral use
- An identifying lot or control number
- A statement directed to the pharmacist specifying the type of container to be used in dispensing the drug (e.g., “Dispense in tight, light-resistant container as defined in the National Formulary”)
- The expiration date, unless exempted (Note: When an expiration date is stated only in month and year, the expiration date is the last day of the month.)

If the container is too small or unable to accommodate a label with space for all the information and is packaged within an outer container, the recommended dosage, route of administration, inactive ingredients, and statement regarding type of container may be contained in other labeling on or within the package. Moreover, the “Rx Only” statement may be placed only on the outer container and the lot number may be printed on the crimp of the dispensing tube.

Unit Dose Labeling
Unit dose packaging is when a single dosage unit of a drug is prepackaged and prelabeled for direct administration. Many hospitals, skilled nursing facilities, and other institutions commonly use unit dose systems because they reduce errors and diversion and permit the return of unused sealed doses. It would not be practical to require the label of a unit dose package to contain the same infor-
The regulations require a label on the unit dose container to include (see Compliance Policy Guide (7132b.10)):

- The established name of the drug
- The quantity of the active ingredient in each dosage unit
- The expiration date
- The lot or control number
- The name or place of business of the manufacturer, packer, or distributor
- Any statements required by a compendia if an official drug, or for unofficial drugs, any pertinent statement regarding special characteristics

The Package Insert

The package insert is a pamphlet that must accompany the drug product and contains the essential scientific and medical information needed for safe and effective use of the drug by health care professionals. It cannot be promotional in nature, false, or misleading. FDA regulations specify not only the contents and format of the prescription drug’s label, but also the package insert and other labeling (21 C.F.R. §§ 201.56, 201.57, and 201.100).

Health care professionals have not found the package insert very useful, and many do not use it as their primary source of drug information. They find that the format and content of the insert make it difficult to read and difficult to distinguish important information and warnings from information clutter and “legalese.” In 2000, after evaluating extensive information and feedback from health care professionals regarding how the content and format of the package insert could be improved to enhance safer and more effective use of prescription drugs, the FDA proposed a regulation to make major revisions in the package insert (see 65 Fed. Reg. 81082, Dec. 22, 2000, and 66 Fed. Reg. 17375-01, March 23, 2001). The FDA made the regulation final in January 2006 (see 71 Fed. Reg. 3922-01; 21 C.F.R. Parts 201, 314, and 601).

The new package insert is designed to reduce preventable adverse drug events by making information about the drug more easily accessible, more memorable, and less complex. The insert reorganizes critical information so that health care professionals can find the information they need quickly. This is accomplished by including a “Highlights” section at the beginning, which summarizes the most important information about the product including Boxed Warnings, Indications and Usage, and Dosage and Administration. The Highlights section will also refer the reader to the appropriate section of the Full Prescribing Information. To ensure health care professionals have the most up-to-date information, manufacturers must include a list of all substantive changes made within the past year.

In order to help health care professionals find critical information more quickly, a Table of Contents has been added. The Full Prescribing Information is reorganized to give more prominence to the most important and most commonly referenced information. In addition, a Patient Counseling Information section has been added, designed as the FDA has stated: “to help doctors advise their patients about important uses and limitations of medications.” It is also hoped that this section will serve as a guide for discussions about potential risks and how to manage those risks. Any FDA-approved patient information is included immediately after the Patient Counseling section.

Unfortunately for health care professionals, the new package insert requirements apply only to drugs whose new drug applications were submitted after June 30, 2006, and will be phased in gradually for drugs approved within the past 5 years. The FDA hopes manufacturers of other drug products will comply voluntarily. Health care professionals do have access to a recent e-Health ini-
Black Box Warnings  When the use of a drug may lead to death or serious injury, the FDA may require the warning of the special problem in the package insert to be placed within a prominently displayed box, also known as a black box warning (21 C.F.R. §201.57(c)(1)). The FDA considers a decision to require a boxed warning to be a dramatic step, and only about 450 prescription drugs contain a black box warning. Despite the prominence of the boxed warning in the insert and the seriousness of the warning, the FDA and most professional organizations agree that they are usually ineffective. Reports indicate that many prescribers are either unaware of the warnings or simply do not heed them. Many drugs (Propulsid and Duract, for example) may not have needed to be withdrawn from the market if health care professionals simply observed and managed the risks contained in the boxed warning. The FDA is hoping that the new revisions to the package insert will improve the effectiveness of the boxed warnings. If not, the FDA will likely require other risk management strategies for high-risk drugs.

Pregnancy Warnings  The labeling regulations also require that the package insert contain information about use of the drug during pregnancy, unless the drug is not absorbed systemically and not known to harm the fetus (21 C.F.R. §201.57(c)(9)). There are five categories of risk in pregnancy into which a drug might be placed:

- **Category A:** Adequate and well-controlled studies in pregnant women have not demonstrated a risk to the fetus. The labeling for drugs in this category must also contain a notice that because studies cannot rule out the possibility of harm, however, the drug should be used during pregnancy “only if clearly needed.”
- **Category B:** Animal studies have failed to demonstrate a risk to the fetus and there are no adequate well-controlled studies in pregnant women. As with Category A, a statement must be included providing that the drug should be used during pregnancy “only if clearly needed.”
- **Category C:** Either animal studies have shown an adverse effect on the fetus or there are no animal reproductive studies, and there are no adequate well-controlled studies in pregnant women. A statement must be included that the drug should be used during pregnancy “only if the potential benefit justifies the potential risk to the fetus.”
- **Category D:** Positive evidence of fetal risk exists based upon data from investigational or marketing experience or studies in humans; however, potential benefits from the drug may be acceptable despite potential risks (for example, in life-threatening or serious disease situations for which a safer drug cannot be used). A statement must be included in the Warnings and Precautions section that the drug can cause fetal harm, and that the patient should be apprised of the risk if pregnant.
- **Category X:** Studies in animals or humans have demonstrated fetal risk, and that risk in pregnant women clearly outweighs any benefit. The Contraindications section must state that the drug “may cause fetal harm when administered to a pregnant woman.” A statement must also be included that the patient should be apprised of the potential hazard to the fetus if used while pregnant. Accutane and Thalidomide are examples of drugs that fall into this category.
National Drug Code Number

A National Drug Code (NDC) number is required on all OTC and prescription drug labels and labeling (21 C.F.R. §§ 201.2 and 207.35). Under the original system, the NDC number contained nine characters, either as numbers or letters. In the 1970s, however, it was changed to a 10-digit number, and the original 9-character codes previously assigned to products received a leading zero. For original NDC numbers, the first four characters of the number identify the manufacturer or distributor, the next four characters identify the drug, and the last two characters identify the package. Today, under the code system assigned to new products, all 10 characters are numbers. The first five digits identify the manufacturer or distributor, and the last five digits identify the drug name, package size, and type of drug. The FDA will switch to an 11-digit code when the first 5-digit code component has been exhausted.

The presence of the NDC number on the label or labeling does not indicate that a drug has received an approved NDA. The FDA assigns the number simply for identification purposes. It has proved invaluable for facilitating the processing of third-party prescription drug claims and for distributing products among manufacturers, wholesalers, and pharmacies.

The regulation requires all human drug and biological labeling to include the NDC number as a linear bar code. The intent of this requirement is to help reduce the number of medication errors by allowing health care professionals to scan the bar code to verify that the right drug, dosage, and route of administration is provided to the patient (69 Fed. Reg. 9120-01, February 26, 2004).

**Study Scenarios and Questions**

1. A pharmacist received a bottle of cephalosporin capsules. Unknown to the pharmacist, the tablets also contained small amounts of penicillin. The pharmacist dispensed the capsules to a patient who is allergic to penicillin and who then suffered an anaphylactic shock. Explain whether the drug is misbranded and/or adulterated. Explain whether the pharmacist has violated the FDCA, and if so, whether the pharmacist might face sanction by the FDA.

2. A hospital pharmacy received ampules of a commonly stocked drug contained in a pink solution. The drug has always been in a clear solution previously. The pharmacist dispensed the drug for IV administration. The drug was contaminated and injured the patient. Explain the difference between this situation and the one in question 1 as related to the pharmacist involved.

3. A pharmacist received a prescription for a brand name drug and legally substituted a generic drug. The pharmacist labeled the dispensed generic drug with the brand name drug. Explain whether the pharmacist has violated the FDCA.

4. A pharmacist received a call from a physician who ordered ibuprofen 600 mg for a patient, but instructed the pharmacist to label the drug as oxycodone. Explain whether the pharmacist would violate the FDCA if he or she complies, and whether this situation differs from question 3.

5. A patient hands a pharmacist a prescription for Spondicin 20 mg, a prescription-only drug. As the patient is waiting for the prescription to be filled, the patient notices that Spondicin 10 mg is available over the counter and asks the pharmacist how it can be that one strength is prescription only and the other is OTC. What should the pharmacist say? Would the pharmacist violate the FDCA by telling the patient to use the OTC drug for the prescribed indication in the prescribed dose when that indication or dosage is not contained in the OTC drug’s labeling?
6. A pharmaceutical manufacturer issued a Class I recall for one of its prescription drug products. How might a pharmacist learn of this recall? Explain whether a pharmacist would violate the FDCA if he or she dispensed the drug after the recall notice. If it is a violation, explain whether it would be a defense if the pharmacist did not know of the recall.

New Drug Approval

The FDCA provides that no person shall introduce into interstate commerce any “new drug,” unless that drug has an approved application by the FDA (Section 505; 21 U.S.C. § 355(a)). If the drug is not a generic of a currently marketed drug, this means that drug manufacturers must apply for and receive FDA approval of a new drug application (NDA), an extremely expensive and lengthy process.

Some of the extensive information that the applicant must provide to the FDA as part of the application includes (Section 505(b)):

- Full reports of investigations showing the drug’s safety and efficacy
- The drug’s components and composition
- The methods, facilities, and controls used in manufacturing, processing, and packaging the drug
- Samples of the drug and its components
- The proposed labeling of the drug

Regarding the safety of the drug, applicants must submit adequate information to demonstrate the drug’s safety for use under the conditions prescribed, recommended, or suggested in the proposed labeling (Section 505(d)). With respect to efficacy, the law stipulates that the applicant must submit “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions or use prescribed, recommended, or suggested in the proposed labeling.” Substantial evidence is defined as the findings of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the drug’s effectiveness (Section 505(d)).

Defining “New Drug”

The FDA must approve every “new drug” prior to marketing, so the question becomes, what is a “new drug”? Section 201(p) of the FDCA defines a “new drug” as a drug that is not generally recognized by qualified experts as safe and effective for use under the conditions recommended in the drug’s labeling. The definition also provides that, even if the drug is so recognized, it must also have been used to a “material extent or for a material time under the conditions recommended in the labeling.” Importantly, a drug marketed before 1938 is exempt from proving either safety or efficacy, provided that it is marketed in accordance with the labeling requirements as then existed.

As will be discussed, some drugs have been marketed for several years without FDA approval. If the FDA ultimately decides that these drugs must now be approved, the new drug definition seems to suggest that a manufacturer should be able to demonstrate that its product is not new and be able to market the drug without going through the NDA process. If the manufacturer can demonstrate that its product is generally recognized by experts as safe and effective (commonly termed GRASE) and has been used to a material extent and for a material time, the drug should not be new.
In actuality this does not happen (except in some instances with OTC drugs). The FDA will not GRASE a product, but rather requires the drug manufacturer to prove safety and efficacy through the NDA process. The manufacturer has no choice but to comply because the courts will not second guess the agency’s decision.

An example of this situation occurred with levothyroxine products. Levothyroxine products had been lawfully marketed for over 40 years without FDA approval until problems surfaced in the 1990s regarding bioavailability and bioequivalence. The FDA thus ordered that all levothyroxine products must have an approved NDA by August 2003. Abbott attempted to convince the FDA that its product, Synthroid, was not a new drug because it had been used safely and effectively for so many years. The FDA rejected the GRASE approach, however, and required Abbott to apply for and ultimately receive an approved NDA.

Approved Drugs as New Drugs

Although typically one thinks of a new drug as some novel and as yet unapproved chemical entity, an approved drug may become a new drug if

- The drug contains a new substance (e.g., active ingredient, excipient, carrier, or coating).
- There is a new combination of approved drugs.
- The proportion of ingredients in combination is changed.
- There is a new intended use for the drug.
- The dosage, method, or duration of administration or application is changed. (21 C.F.R. § 310.3(h))

It is not always obvious when an approved drug will become a new drug. In United States v. Baxter Healthcare Corporation, 901 F.2d 1401 (7th Cir. 1990), the court considered whether reconstituting, repackaging, freezing, and distributing approved antibiotic drugs make them new drugs. Baxter owned a compounding center that performed these functions on antibiotic powders and concentrates to prepare them for immediate use by health care providers. Baxter argued that it simply prepared the drugs according to the label instructions exactly as a physician or pharmacist would and, thus, the drugs could not be new drugs. Giving great deference to the judgment of the FDA, however, the court found that the reconstitution did indeed make the drugs new drugs because the procedure raised concerns about the safety and efficacy of the final product. To support its conclusion, the court referred to the statute and regulations that require a full description of the methods, facilities, and controls used in manufacturing, processing, and packaging with the submission of an NDA.

The Road to an Approved New Drug Application

In seeking approval for an NDA, an applicant must submit evidence (pursuant to § 505(d)) that the drug is safe and effective. This evidence must be obtained through animal and clinical (human) studies. Section 505(a), however, forbids the shipment of any new drug unless the drug has an approved NDA. This seemingly contradictory situation is avoided by section 505(i), which allows the FDA to exempt a drug from the NDA requirement for the pursuit of clinical investigations. To receive this exemption, the manufacturer must apply for a “Notice of Claimed Investigational Exemption for a New Drug,” commonly called an Investigational New Drug (IND) Application. If approved, the manufacturer may then conduct clinical studies of its investigational new drug. Application of an IND follows extensive preclinical investigation by the applicant, where through laboratory experi-
Investigational New Drug Application

The law requires a manufacturer seeking IND approval to submit a substantial amount of information, including:

- The name of the drug
- Its composition
- Methods of manufacture and quality control
- Information from preclinical (animal) investigations regarding pharmacological, pharmacokinetic, and toxicological evaluations

The application must also include information about the experience and qualifications of the clinical investigators, as well as a complete outline of the proposed clinical trials. The primary purpose of the approval process for an IND is to protect the safety of the humans who will participate in the clinical trials. Secondarily, the process is intended to ensure that the clinical studies are designed properly so as to prevent problems during the NDA review.

If the FDA does not reject the IND request within 30 days of submission, human clinical testing may begin. The testing proceeds through three phases. In phase 1, which involves a small number of subjects, investigators examine the drug’s toxicity, metabolism, bioavailability, elimination, and other pharmacological actions. Doses of the drug are initially low, then gradually increased. The purpose of phase 1 is to detect adverse effects, not to determine efficacy.

If the drug passes phase 1, it moves to phase 2, where it is tested on a limited number of patients who actually have the disease for which the drug is an intended treatment. The purpose of phase 2 is to determine the efficacy of the drug and the dosages at which the efficacy occurs. Investigators also continue to conduct pharmacological testing to determine further the drug’s safety.

If the drug’s safety and efficacy appear promising, the study proceeds to phase 3, where the drug is tested for safety and efficacy in hundreds or even thousands of patients. These tests often occur in actual clinical settings, such as physicians’ offices and hospitals that have contracted with the manufacturer to conduct the studies. Usually, the studies are double-blinded and compared with a control group that receives a placebo.

The FDA may terminate the testing of an IND at any time if studies show that the drug is too toxic under the agency’s benefit/risk ratio criteria. The FDA’s determination is final and not subject to appeal or judicial review. If the phase 3 study results are favorable, the drug’s sponsor may submit an NDA to the FDA. Only about 1 in 10 drugs demonstrates enough merit to make it this far in the process, however.

Informed Consent

In all three IND clinical phases, the FDCA (section 505(i)) requires the investigators to secure the informed consent of the patient or a representative for the administration of an experimental drug. This requires that potential participants know the risks, possible benefits, and alternative courses of treatment. In addition, if the study is to take place in an institutional setting, the local institutional review board (IRB) must approve the study. An IRB is a committee designated by the institution charged with reviewing any research projects involving human subjects.

The patient’s consent must be in writing in phases 1 and 2. In phase 3, patient consent may be oral if the physician decides it is necessary or it is preferable to written consent, and this decision is
recorded in the patient’s medical record. Patient consent may not be necessary when it is not feasible to obtain the consent of the patient or a representative, or when, in the professional judgment of the physician, informed consent is not in the best interest of the patient.

The New Drug Application

As a compilation of all information obtained during the IND process, an NDA contains a complete evaluation of the drug’s safety and efficacy. There may be 100,000 to 200,000 pages of summary and raw data. This information includes, in part, details of drug chemistry, preclinical studies, manufacturing processes, clinical studies, labeling, and packaging. In all, an NDA has five to six technical sections, each to be reviewed by an expert in that scientific discipline.

By statute, the FDA has 180 days in which to act on a completed NDA, but significant delays are common (§ 505(c)(1)). Manufacturers will rarely launch a legal challenge against the FDA to expedite action, preferring cooperation and realizing that lengthy litigation would be self-defeating. The potential importance of the drug usually dictates the length of approval time. Proof of the drug’s safety and efficacy, the proposed manufacturing process, and benefit/risk ratio generally determine whether the FDA will approve an NDA. If the FDA proposes to disapprove an NDA, it will notify the applicant and provide the applicant with an opportunity for a hearing. Although the applicant may judicially contest the FDA’s determination to refuse to approve an NDA, no applicant has ever succeeded in court.

The Prescription Drug User Fee Act of 1992 (PDUFA) is generally credited as having reduced the FDA review time for NDAs from a median approval time of 23 months before the act to 15 months for 1995. The law, by requiring substantial user fees from product sponsors, accomplishes this purpose in two ways: First, the fees allow the FDA to hire hundreds of extra reviewers. Second, the high fees discourage sponsors from submitting applications until they have a high probability of success, reducing the review effort required.

FDA Drug Rating and Classification System

Since 1974, the FDA has used a priority classification system that rates new drugs by chemical type and therapeutic potential. The rating assigned to a drug determines how rapidly it will proceed through the NDA process. Usually, FDA reviewers assign a rating when the IND request is made, but the rating may be changed during the subsequent approval process. The rating of an approved drug is often important because physicians and pharmacists may consider it when evaluating new drug therapies and making drug formulary decisions.

In the FDA classification system, a number indicates the drug’s chemical type; a letter indicates its therapeutic potential. For chemical type, the six designations are:

1. The active moiety is a new molecular entity.
2. The active moiety is in a new salt or ester form.
3. The dosage form or formulation is new.
4. The product is a new combination of compounds.
5. The drug product is essentially a duplicate of another drug product.
6. The drug is a product previously marketed by the same firm (used primarily for new indications).

These types are not mutually exclusive because a new formulation (type 3) or a new combination (type 4) may also contain a new molecular entity (type 1) or a new salt (type 2).
For therapeutic potential, the FDA uses the letters P for priority or S for standard (replacing the A, B, and C letter ratings used before 1992). A rating of P indicates that the drug may represent a therapeutic advance for one or more of these reasons:

- No other effective drugs are available.
- It is more effective or safer than drugs currently used.
- It has important advantages, such as greater convenience, reduced side effects, or improved tolerance or usefulness in special populations.

An S rating means that the drug may have therapeutic properties similar to those of drugs already on the market.

**Supplemental New Drug Applications**

After the approval of an NDA, a manufacturer may not usually make any changes in the drug or its production, even the most minor ones, unless it submits for approval a supplemental NDA (21 C.F.R. § 314.70). Depending on the type of change intended, a supplemental NDA falls into one of three procedural categories. For changes in any part of the production, ranging from the synthesis of the drug, to the manufacturing processes of the drug, to most of the labeling of the drug, a “prior approval” supplement is required, whereby the agency must approve the change before the sponsor can implement it. For certain types of labeling changes such as those that strengthen warnings or dosage and administration information, or for certain changes in manufacturing methods, facilities, and controls, a “change being effected” supplement may be allowed. This type of supplement allows the sponsor to implement the change before the FDA approves it. The final category of supplemental NDA allows very minor changes, such as editorial changes in labeling or changes in container size to merely be reported in the annual report that the sponsor must file to the FDA.

Supplemental NDAs requiring preapproval usually have a lower priority than do original NDAs and, thus, may take years to be approved. A manufacturer may, however, ask the FDA to expedite its review “if a delay in making the change described in it would impose an extraordinary hardship on the applicant.”

**Postmarketing Surveillance**

Once the new drug application has been approved, the manufacturer may legally distribute the drug in interstate commerce. Section 505(k) of the FDCA, however, requires that the manufacturer maintain and establish postmarketing records and reports. Under this provision, the manufacturer must submit to the FDA reports of any serious adverse drug reactions (21 C.F.R. § 314.80) and any new information relating to the drug’s safety and efficacy (21 C.F.R. § 314.81), including information about current clinical studies, the quantity of drug distributed, labeling, and advertising. This postmarketing surveillance is necessary for two reasons. First, an investigational drug is tested in a relatively small number of patients compared with the number of patients who may use the drug after it is marketed; second, long-term adverse effects may not be discoverable before approval. As a result of postmarketing information, the FDA may withdraw its approval of an NDA and, in fact, has done so on some occasions.

**Phase 4 Studies**

As part of the postmarketing surveillance activities, the FDA has historically required that product manufacturers conduct clinical studies after the drug is approved, commonly called phase IV
studies. Although the agency lacked clear statutory authority to require phase IV testing in the past, the FDAMA now gives the FDA that authority for “fast-track” drug approval, as discussed later in this chapter. The major objectives of phase IV studies are to obtain additional data regarding the drug’s safety and effectiveness and determine new uses for or abuses of the drug.

Drug Efficacy Study Implementation

The FDA initiated the Drug Efficacy Study Implementation (DESI) program in 1968 in response to the 1962 amendment requiring that drugs be effective as well as safe. The FDA applied the efficacy requirement retroactively to all drugs marketed after 1938 (pioneer drugs as well as generic drugs). Until the efficacy requirement was added, the FDA had established an informal policy of allowing many post-1938 generics to be marketed as not new drugs to facilitate generic competition. The FDA considered these generics as “generally recognized” as safe if the pioneer drug had a safe marketing history. Under DESI, however, the FDA now regarded the generic drugs as new drugs, and required generic manufacturers to prove efficacy. Several drug manufacturers balked at having to establish efficacy for their currently marketed drug products and contested the legality of the government action. However, in three 1973 decisions (Ciba Corporation v. Weinberger, 412 U.S. 640; Weinberger v. Bentex Pharmaceuticals, Inc, 412 U.S. 645; and USV Pharmaceutical Corporation v. Weinberger, 412 U.S. 655), the U.S. Supreme Court upheld the retroactive efficacy requirement for drugs, as well as the FDA’s authority to determine whether a drug is a new drug.

Making proof of efficacy retroactive to innovator and generic drugs burdened the FDA with the responsibility for evaluating the efficacy of the several thousand drugs that had been approved between 1938 and 1962. To obtain some assistance with this overwhelming project, the FDA commissioned the National Academy of Sciences National Research Council to study the drugs and submit its recommendations. The National Academy divided the task among 30 panels of experts within specific drug categories. Each drug was to be classified into one of six categories:

1. Effective
2. Probably effective (additional evidence required)
3. Possibly effective (little evidence submitted)
4. Ineffective (no acceptable evidence)
5. Effective, but... (effective but better, safer, or more conveniently administered drugs are available)
6. Ineffective as a fixed combination

To further lighten its burden, rather than requiring NDAs for generic drugs, the FDA created a new form of NDA, called an abbreviated new drug application (ANDA). Under an ANDA, proof of safety and efficacy was not required, but rather only proof of bioequivalence and proof of acceptable manufacturing methods and controls. Because the agency became swamped with ANDA proposals, it began allowing manufacturers of generic drugs to continue to market their products pending the approval of their ANDAs. This practice prompted a lawsuit, Hoffman LaRoche, Inc. v. Weinberger, 425 F. Supp. 890 (D.D.C. 1975), in which a U.S. district court held that the FDA could not allow drugs to be marketed unless their ANDAs or NDAs had been approved.

The court ruling frustrated certain generic manufacturers who faced substantial economic losses if they could no longer market their products. Some of these manufacturers ignored the ruling and continued to market their generic drugs, prompting the FDA to seize some of their products. The manufacturers then sued the FDA. In United States v. Articles of Drug... Lannett Co., 585 F.2d 575 (3rd Cir. 1978), and Premo Pharmaceutical Laboratories, Inc. v. United States, 629 F.2d 795 (2nd Cir.
1980), the generic manufacturers raised a very interesting argument, contending that because the active ingredients in the parent drugs had already been approved as safe and effective, their generic drugs were not new drugs. Therefore, they advanced, the FDA had no statutory authority to withhold the approval of generic drugs. The FDA countered that new drug status is warranted for generic drugs because their safety and efficacy cannot be determined until such questions as the methods of manufacture and proof of bioequivalence are answered. Federal courts reached contrary decisions on this issue until the U.S. Supreme Court finally determined in United States v. Generix Drug Corporation, 103 S. Ct. 1298 (1983), that a generic drug is a new drug, thus subject to FDA approval.

"Paper" New Drug Applications

Although the FDA would accept ANDAs for generic drug equivalents marketed between 1938 and 1962, it did not accept ANDAs for generic equivalents marketed after 1962. The FDA held the position that it lacked statutory authority to do so. Recognizing the inconsistency of allowing ANDAs for pre-1962 generic drugs, but requiring only NDAs for post-1962 generic drugs, the FDA compromised by implementing its “paper” NDA policy in the late 1970s. Under this policy, a generic drug manufacturer would not have to duplicate the actual research establishing the safety and efficacy of the innovator drug, as a full NDA would require. Rather, the generic drug manufacturer could submit evidence of its drug’s safety and efficacy on the basis of the published scientific data generated from the innovator manufacturer’s studies. Needless to say, innovator drug manufacturers were not pleased with this policy and judicially challenged the practice of “paper” NDAs in Burroughs Wellcome Co. v. Schweiker, 649 F.2d 221 (4th Cir. 1981), but the FDA prevailed. Nonetheless, the policy helped only a small number of post-1962 generic drugs because there was seldom enough published literature to support the manufacturer’s claims of safety and efficacy for the drug. Clearly, a legislative solution was needed, and that solution came in the form of an amendment to the FDCA in 1984 called the Drug Price Competition and Patent Term Restoration Act (PTRA), as discussed next.

Drug Price Competition and Patent Term Restoration Act (PTRA) of 1984

Essentially, the PTRA (P.L. 98-417) codifies the FDA’s ANDA policy for pre-1962 drugs. Because the law streamlines the approval process for generic drugs, manufacturers can market them more quickly under an ANDA. As discussed previously, under an ANDA, a manufacturer does not have to conduct clinical studies to establish safety and efficacy. Rather, the sponsor needs only to submit sufficient information to demonstrate that the generic is bioequivalent to the pioneer drug and that it has acceptable manufacturing methods and control procedures. The FDCA allows the presumption that if the products are bioequivalent then the generic drug is as safe and effective as the innovator drug.

Bioequivalence must usually be established through evidence obtained from human clinical trials establishing either that the generic drug’s extent of absorption (maximum concentration, Cmax) and rate of absorption (area under the curve, AUC) at the site of action are not significantly different from those of the pioneer drug or that the extent of absorption is the same and the rate of absorption is intentionally different, as long as the difference is not essential to attaining effective drug concentrations in the body and is considered medically insignificant for the drug. The different rate of absorption must be reflected in the drug’s labeling. A company is not required to conduct clinical trials to establish bioequivalence if the FDA can conclude bioequivalence from other studies or other facts submitted by the company.

The significant statutory concession for generic drug manufacturers was not without comparable concessions for innovator drug manufacturers. The law allows the FDA to grant innovator drugs
either patent-term extensions or market exclusivity for 2 to 5 years, depending on when the regulatory review of the drug began and how much time it required. The innovator drug manufacturers lobbied hard for patent extensions and extended market exclusivity because their products normally receive patents long before the products are ultimately approved for marketing. As a result, often only a few of the 20 years granted for patent protection remain after the drug is marketed. Patent extensions are available only if the patent has not expired. Market exclusivity, on the other hand, works independently of the drug’s patent status. In general, for new chemical entities approved under an NDA, the market exclusivity provision prevents a generic drug application from being submitted for 5 years from the date of approval of the drug.

The PTRA created two controversies for health care practitioners. First, the law allows a generic drug to statistically vary in its rate and extent of absorption by plus or minus 20 percent from the parent and still be considered as bioequivalent. This led to the position that if a patient used generic X 1 month, which was plus 20 percent, and generic B the next month, which was minus 20 percent, there could be a 40 percent blood level difference between the two products, resulting in adverse clinical outcomes for the patient. The FDA countered this concern in public announcements by clarifying the statistical procedure involved. It further provided that in analyzing data on generic drugs approved between October 1984 and September 1986, the average difference in absorption between generic and pioneer products was only plus or minus 3.5 percent, which should not produce clinical differences in patients. Nonetheless, the controversy continues for some drug products.

The second controversy created by the act centered on the substitution of a generic drug for the parent when the manufacturer of the parent drug retained marketing exclusivity over certain indications, yet both products were legally on the market. For example, can a pharmacist legally substitute a generic propranolol prescribed for postmyocardial infarction when the innovator brand propranolol has marketing exclusivity for that indication? The general answer to this question is yes because this is really the use of an approved drug (the generic drug) for an off-label indication, as discussed in Chapter 3. (Chapter 3 will address how issues of bioequivalence, drug substitution, and off-label indications affect pharmacy practice.)

A separate but related issue is whether the FDA can legally approve an ANDA for a new generic drug even though the labeling of the generic product will not include one or more of the indications appearing on the labeling of the innovator (parent) drug because of the exclusivity provisions. (The law provides that the labeling of the generic drug must be the same as that of the innovator drug. This creates a dilemma, however, because if the innovator drug has exclusivity over certain indications, those indications could not be included in the generic drug’s labeling.) The federal court in Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493 (D.C. Cir. 1996) held that the FDA indeed could still approve the ANDA for a new generic drug, despite the fact that the manufacturer held exclusivity rights for 3 years to an indication approved by supplemental application and that this indication is not included on the generic’s labeling. (Indications approved by supplemental application to an NDA are granted 3-year exclusivity under PTRA.) Bristol-Myers argued that the statute, § 355(j)(2)(A)(v), requires that the generic label be “the same” as that of the innovator and because it cannot be the same, the ANDA must be rejected. The court, however, agreed with the government’s analysis that the manufacturer’s interpretation is at variance with other provisions in the law and legislative intent, that being that the new generic drug be safe and effective for each indication appearing on the label. The fact that the label does not list every indication listed on the pioneer’s label is irrelevant. Even more persuasive to the court, however, was the fact that if Bristol-Myers’s interpretation prevailed, a new generic drug product would be precluded from the market for 3 years every time a manufacturer added a supplemental indication. Theoretically, then, the manufacturer of a pioneer drug could strategically file supplemental indications over several years, precluding any generic competition.
Section 505(b)(2) NDAs (The New Paper NDA)

The PTRA not only statutorily created the ANDA, but also established what is known as a 505(b)(2) application. Very similar to the old paper NDA, under this application the applicant is allowed to rely upon safety and efficacy data furnished by another applicant—even unpublished data that are not legally protected. The 505(b)(2) application has received considerable notoriety in recent years as manufacturers have used it to apply for new indications of established drugs, relying upon safety reports in a previous NDA.

Over-the-Counter (OTC) Drug Review

The 1962 efficacy requirement retroactively applied not only to prescription drugs for which NDAs had been approved, but also to OTC drugs. As a result, after 10 years of attention to prescription drugs under the DESI review, the FDA began reviewing OTC drugs marketed between 1938 and 1962. Although the FDA examined the efficacy of each prescription drug on a case-by-case basis in the DESI review, the agency initiated a different system to review OTC drugs. This system, which continues today for post-1962 OTC products, evaluates OTC products on the basis of therapeutic category, rather than individually, and classifies products through rule making rather than on a case-by-case basis. The agency took this approach for several reasons. First, there were between 100,000 and 500,000 OTC drug products on the market, many of which did not have approved NDAs; reviewing each of these products would overwhelm the FDA's resources. Second, litigation to remove unsafe or ineffective individual OTC products would be prohibitively time-consuming and expensive. Third, nearly all the OTC drugs were prepared from only about 200 active ingredients.

Under the procedures for classifying OTC drugs as safe and effective (21 C.F.R. Part 330), the FDA appoints advisory review panels of qualified experts to consider the drugs by class (e.g., analgesics, antacids) and to make recommendations to the agency. The FDA then publishes the panels' recommendations in the Federal Register, requesting public comment. After receiving public comments, the agency issues a proposed rule in the Federal Register. Then, the agency publishes a monograph, identifying which active ingredients are generally recognized as safe and effective and, thus, may be marketed. The monograph further specifies the labeling. Products that do not contain approved active ingredients or labeling must be removed and, if possible, reformulated and relabeled. Alternatively, the manufacturer of a product that does not conform to the criteria in the monograph may withdraw the product and follow the NDA procedures or petition to amend the monograph. New OTC drug products that conform to the published monograph requirements may be marketed without FDA approval.

The final monograph on a reviewed ingredient specifies in which of three categories the ingredient is placed:

1. Category I includes ingredients generally recognized as safe, effective, and not misbranded.
2. Category II includes those ingredients that are not generally recognized as safe and effective or that are misbranded.
3. Category III includes ingredients for which data available are insufficient to permit classification.

Since the implementation of the OTC drug review, the FDA has allowed by regulation the continued marketing of drugs placed in category III until evidence was sufficient to place them in categories I or II. Otherwise, the FDA feared, drug manufacturers would not submit their products for review, and the FDA would be forced to bring new drug litigation against each product. In Cutler v. Kennedy, 475 F. Supp. 838 (D.D.C. 1979), however, a group of consumers contested the FDA's policy...
and demanded that the FDA remove all category III products from the market. The court agreed with
the plaintiffs that an FDA regulation allowing these OTC drugs to be marketed pending the agency’s
determination of safety and efficacy was an affront to the FDCA’s premarketing procedures. Al-
though the court concluded that the FDA did not have the authority to continue this practice, the
court disagreed with the plaintiff’s claim that the FDA must seek out and remove category III drugs
from the market, finding that there was no statutory ultimatum for this action. In effect, the Cutler
decision caused the FDA to revise its regulations but to continue informally to do what it had been
doing by regulation.

Marketed Unapproved Drugs

Based upon the preceding discussions, one might be led to believe that except for some drugs mar-
keted prior to 1938, all marketed drugs today have been approved by the FDA. For various reasons,
however, this is not the case. In fact, in a compliance policy guide published in June 2006, the FDA es-
timated that there are as many as several thousand prescription and OTC drug products marketed il-
legally without required FDA approval. (See U.S. Department of Health and Human Services, 2006.)

There are many reasons why this situation exists:

1. Recall in the DESI discussion that until DESI was instituted in 1968, the FDA had a policy
of allowing many post-1938 generics to be marketed as not “new drugs” if the pioneer or
innovator drug had a safe marketing history.
2. During that same time period, the FDA allowed some drugs to be marketed that were not
identical or similar to other marketed drugs, either on the basis that the FDA felt that they
were not new drugs or simply because the agency did not take action against them.
3. Some drugs are still being marketed pending a final determination of their efficacy under
DESI reviews. (Technically these drugs should not be considered illegally marketed because
the FDA has allowed the products to be marketed pending DESI review.)
4. Some products that have been determined to lack evidence of efficacy after DESI review
have yet to be removed from market.
5. Some similar drugs to the products pending DESI review, which have never submitted ap-
plications for review, remain on the market.
6. Many drugs are being marketed claiming to be grandfathered as pre-1938 drugs, yet have
changed labeling or composition, thus voiding their exemption status.
7. Some drug manufacturers simply market their product without approval, hoping to get
away with it for as long as possible.
8. There are illegally marketed OTC drugs either because monographs do not allow their in-
gredients or because they were never subject to the OTC review.

In the compliance policy guide the agency explains that these illegally marketed drugs remain on
the market because first they have to be identified (no easy process), and then to remove each prod-
uct requires a considerable amount of scarce FDA resources and time in order to comply with legal
procedures. As a result, the FDA prioritizes enforcement, with highest priority going to drugs that
present safety risks, those that lack evidence of effectiveness, and those that involve health fraud. The
agency noted that it might bring enforcement action against a product without notice.

The FDA will more likely take enforcement action against unapproved identical or similar prod-
ucts when one manufacturer obtains NDA approval for its product. The agency stated it will allow
a one-year grace period from the date of NDA approval before it will initiate enforcement action against the unapproved products of the same type. The one-year grace period, however, is dependent upon various factors and will be determined on a case-by-case basis. Pharmacists should exercise professional judgment when dispensing drugs of a particular type where one is approved and the others are not. From a risk management perspective, it might generally be wise to dispense the approved product.

**Drugs Intended to Treat Serious and Life-Threatening Diseases**

Over the years, the new drug approval process and the FDA have been criticized for denying or impeding access to new drugs for people with serious and life-threatening diseases for which no other treatment exists. In *United States v. Rutherford*, 442 U.S. 544 (1979), reported in the case studies section, terminally ill patients unsuccessfully sued the FDA in an attempt to obtain an unapproved drug for cancer treatment. The FDA continually faces the dilemma of expediting patient access to drugs intended to treat these conditions, while protecting patients against unsafe, ineffective, or even fraudulent products.

The FDA has not been unsympathetic to the plight of those with life-threatening diseases. In recent years, it has modified its policy by enacting regulations with respect to both patient treatment with investigational drugs and drug approval for potentially lifesaving drugs. These regulations were essentially codified and replaced by the FDAMA, as discussed here.

**Patient Treatment with Investigational Drugs (§ 561)**

The FDA had long held the position that investigational drugs must be used only for experimentation, not treatment. That position changed, however, as the incidence of acquired immune deficiency syndrome (AIDS) skyrocketed in the United States and researchers began to develop new drugs that showed promise for treating this and other serious diseases. The FDAMA modified the FDCA to state that an investigational drug may be provided for widespread access outside controlled clinical trials to treat patients with serious or immediately life-threatening diseases for which no comparable or satisfactory alternative therapy is available. The FDA will approve the investigational drug for treatment only if:

1. It is to be used for a serious or immediately life-threatening disease or condition.
2. There is no comparable or satisfactory alternative therapy available.
3. The drug is under investigation for the disease or condition.
4. The sponsor is actively pursuing marketing approval of the drug.
5. In the case of serious diseases, there is sufficient evidence of safety and effectiveness for the use.
6. In the case of immediately life-threatening diseases, there is a reasonable basis to conclude that the drug may be effective and would not expose patients to unreasonable and significant risk.

**Individual Patient Access to Investigational Drugs for Serious Diseases (Parallel Track Policy) (§ 561)**

With respect to investigational drugs, the FDAMA also provides that an individual patient acting through a physician may request an investigational drug from the manufacturer if the physician
determines that the patient has no comparable or satisfactory alternative therapy and that the risk to the patient from the drug is no greater than the risk from the disease or condition. To qualify, the FDA must determine that there is sufficient evidence of safety and effectiveness to support its use and that use of the drug will not interfere with clinical investigations in support of marketing approval. The sponsor must also submit to the FDA a protocol describing the use of the drug.

FDA policy has restricted the medical treatment with an IND to those drugs in Phase 3 of the NDA process. A public interest group, formed on behalf of terminally ill patients, sued to enjoin the FDA from enforcing this policy and thus allow terminally ill, mentally competent adults, acting on a doctor’s advice, to obtain IND drugs that have reached Phase 2 (Abigail Alliance for Better Access to Developmental Drugs and Washington Legal Foundation v. Eschenbach, 445 F.3d 470 (C.A.D.C. 2006)). The District of Columbia Court of Appeals reversed and remanded the district court’s decision, finding for the plaintiffs. The court of appeals concluded that terminally ill, mentally competent adults have a protected liberty interest under the Due Process Clause of the Constitution to IND drugs in Phase 2 when there are no alternative approved treatment options available. The court relied heavily on the U.S. Supreme Court decision of Cruzan v. Director, Missouri Department of Health, 497 U.S. 261 (1990), holding that an individual has a due process right to refuse life-sustaining medical treatment. The court could find no substantial difference between the due process right in Cruzan and the one plaintiff’s sought in this case because both involve the right of the individual to the “possession and control of his own person...” (at p. 484).

On December 11, 2006, without mentioning the Abigail decision, the FDA announced a proposed regulation to make experimental drugs more widely available to seriously ill patients with no other treatment options (http://www.fda.gov/cder/regulatory/applications/IND_PR.htm). Under the new regulation, access to experimental drugs even in phase 1 would be available to individual patients, as well as small patient groups and larger populations.

**Expedited Approval of Drugs Intended to Treat Life-Threatening Illnesses (“Fast Track Approval”) (§ 506)**

Motivated primarily by the AIDS epidemic, the FDA enacted regulations in 1988 and 1992 (21 C.F.R. § 312.80–312.88, modified by § 314.50) to expedite the development, evaluation, and marketing of new drugs intended to treat serious or life-threatening illnesses. The substance of these regulations has been codified by the FDAMA, which generally provides that at the request of a new drug’s sponsor, the FDA will expedite the review of the drug (1) if it is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet medical needs for the condition; and (2) the product has an effect on a clinical endpoint or on a surrogate endpoint reasonably likely to predict clinical benefit. Approval will be conditioned on the completion of post-marketing, or phase 4, clinical studies to verify and describe the drug’s clinical benefit. The drug’s sponsor must submit all promotional materials for FDA approval at least 30 days before dissemination. The FDA may use expedited procedures to remove the drug if phase IV studies do not confirm the drug’s safety and effectiveness.

**Biologics**

Biologics or biologicals are products derived from living organisms, and include viruses, therapeutic serums, toxins, antitoxins, vaccines, blood and blood components, and derivatives applicable to the prevention, treatment, or cure of a disease or condition of humans (42 U.S.C. § 262(i)). Biological products have had a history of government regulation since 1902 (four years prior to the first federal
drug law) and today are regulated under both the Public Health Service Act (PHSA) and the FDCA. Although biological products require premarket approval by the FDA like new drug products, unlike drugs biologicals are licensed under the PHSA. The FDA will approve a license upon demonstration that the product is safe, pure, and potent, and that the facility meets required standards. If a biological product contains a drug, it will be classified as either a biological or a drug depending upon the product’s primary mode of action.

Perhaps the most significant difference between the regulation of drugs and biologics is that the law does not appear to allow for generic biological products. The FDA has noted that Congressional legislation would be required, and that making generic versions of biologics would be much more difficult than for drugs. Current science may not be adequate to assure safety and efficacy under an IND process for biological products. For many of these products the manufacturing process is very complex and involves numerous steps. Often, it is not even known which of the components are the active ingredient(s), and efficacy may be a sum of the parts rather than a particular component.

### MedWatch Voluntary Reporting Program

The FDA maintains a voluntary reporting system called MedWatch that allows health care professionals to report any serious adverse events, potential and actual product use errors, and product quality problems related to drugs, biologics, medical devices, special nutritional products, and cosmetics directly to the agency. An official reporting form (FDA 3500) can be accessed and completed online at [https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm](https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm). Pharmacists submit the largest number of adverse drug reaction reports, and are urged to report any problem with a drug product, including improper labeling, the presence of foreign or particulate matter, imperfectly manufactured dosage forms, abnormal color or taste, and questionable stability. The FDA emphasizes that it is the moral obligation of health care professionals to furnish the agency with information about suspected adverse events, product quality problems, and product errors. The agency encourages practitioners to submit reports, pointing out that a report is not a legal claim, nor an acknowledgment that there is an adverse event, problem, or error. The identities of the practitioners and the patients are confidential.

In addition to reports related to drugs, biologics, and devices, the FDA requests practitioners to submit reports of clinically significant toxicity that may be related to the ingestion of substantial quantities of nutrients or food components in dietary supplements, including vitamins and minerals. It also seeks reports of severe and well-documented nonmicrobiological reactions associated with food and food additives.

The MedWatch program not only provides for reporting, but also provides a wealth of safety information on products, accessible from its website at [http://www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### Medical Device Act (Amendments) of 1976

Before 1976, the adulteration and misbranding provisions of the FDCA did not provide the FDA with enough authority to protect the public adequately in the face of a proliferation of quack products and the advances in sophisticated device technologies. As a result, Congress enacted the Medical Device Act of 1976, amending the FDCA to establish a comprehensive system of device regulation that includes device classification, premarket testing, and standards of performance. Devices...
marketed before the act, called “preamendment devices,” were permitted to remain on the market pending classification or other type of action by the FDA.

Pursuant to the device amendments, the FDA must classify all devices into one of three classes.

1. Class I devices require the least regulation because they pose the least potential harm to users; therefore, “general controls” are adequate to ensure safety and effectiveness. General controls require that device manufacturers register their facility and list their products with the FDA, provide premarket notification in some cases, maintain records and reports, and adhere to good manufacturing practices. These devices include needles, scissors, examination gloves, stethoscopes, and toothbrushes.

2. Class II devices are those for which general controls alone are insufficient to ensure safety and effectiveness. These products must meet specific performance standards established by the FDA. Such products include insulin syringes, infusion pumps, thermometers, diagnostic reagents, tampons, and electric heating pads.

3. Class III devices must have premarket approval because they are life-supporting or life-sustaining or they present a potential unreasonable risk of illness or injury. Class III devices include pacemakers, soft contact lenses, and replacement heart valves. Any devices not marketed before 1976 initially fall into class III, unless the FDA determines that they are substantially equivalent to a class I or II device.

Like certain drugs, certain devices may be available by prescription only. Under the law, these are devices that have a potential for harm or require collateral measures to ensure their proper use. Examples of restricted devices include diaphragms and contact lenses.

Custom devices ordered by health care professionals to meet the special needs of individual patients, such as orthopedic footwear, are generally exempt from some requirements such as registration, performance standards, and premarket approval. Other general control requirements do apply, however, such as conforming to good manufacturing practices and the adulteration and misbranding provisions.

The FDA can reclassify devices on the basis of new information of safety and efficacy, and has reclassified hundreds of devices from class III to class II and from class II to class I. If a manufacturer’s petition for reclassification is approved, the reclassification applies to the generic type of device, not just the specific device in question. Thus, the reclassification will benefit not only the particular manufacturer, but also its competitors.

Medical device firms must report to the FDA any death or serious injury that may be related to their products. If the FDA determines that a device presents an unreasonable risk of substantial harm, it may require the manufacturer to notify all health care professionals or to recall the product. If this action is insufficient, the FDA may require the manufacturer to (1) repair the device, (2) replace the device, or (3) refund the purchase price of the device. Alternately, the FDA can seize medical devices, enjoin shipment, and withdraw marketing approval to protect the public.

In 1990, Congress amended the FDCA device provisions of section 519(b) by enacting a law that requires device-user facilities and distributors to report to the Secretary of Health and Human Services any death, serious injury, or serious illness that may be related to the product (Safe Medical Devices Act of 1990). A device-user facility is defined as “a hospital, ambulatory surgical facility, nursing home, or outpatient treatment facility which is not a physician’s office.” Before this law, only manufacturers were required to report adverse incidents. This law was modified and expanded in 1992 (P.L. 102-300). Subsequently, the FDAMA has removed the requirement that distributors must submit adverse event reports to the FDA or to device manufacturers. Distributors must, however, maintain records of adverse events.
Cosmetics

Sections 601 to 603 of the FDCA and 21 C.F.R. Parts 700 to 740 regulate cosmetics. Cosmetics do not have the same stringent legal requirements that drugs and devices have. Premarket approval from the FDA is not necessary for a cosmetic, although manufacturers must substantiate the safety of their cosmetic product and each of its ingredients. Moreover, the manufacturer of a cosmetic does not have to conform to current good manufacturing practices or even register with the FDA; registration is voluntary. The FDA may, however, remove a cosmetic from the market if it is misbranded, adulterated, or determined to be a health hazard.

A cosmetic must be labeled with a list of its ingredients in descending order of predominance. Fragrances or flavors may simply be listed as “fragrances” or “flavors.” The ingredients must be placed on the outside of the package or container so that the consumer can read them at the point of purchase. This information is especially important to consumers with allergies to certain ingredients.

Some cosmetics must have specified warning statements. For example, cosmetics in self-pressurized containers must contain the warning: “Intentional misuse by deliberately concentrating and inhaling contents can be harmful or fatal.”

A cosmetic may be misbranded if its labeling is false, misleads the consumer, or lacks the required information, or if the label information is not clear enough to be read and understood by an ordinary consumer. In addition, the product may be deemed misbranded if the container is made or filled so as to be misleading or if the packaging and labeling do not conform to the requirements of the Poison Prevention Packaging Act (discussed in Chapter 3). If substantiation of the product’s safety is not available, the principal display panel must contain: “Warning—The safety of this product has not been determined,” or the product will be deemed misbranded.

A cosmetic is adulterated if

- It contains any poisonous or deleterious substances that may injure users
- It contains any filthy, putrid, or decomposed substance
- It was prepared under unsanitary conditions
- The container contains a substance that may contaminate the contents
- It contains an unsafe color additive but is not a hair dye

Hair dyes that contain coal tar are exempt from the adulteration and color additive provisions of the law, even though coal tar is an irritant to many users. The product with coal tar must have a warning label, stating

Caution—this product contains certain ingredients that may cause skin irritation on certain individuals, and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

**STUDY SCENARIOS AND QUESTIONS**

1. A drug manufacturer wishes to market its approved drug for use in a disease for which it has not been approved (off-label use). Explain whether marketing the drug for this use would make it a new drug.

2. A patient who has been prescribed a newly marketed drug complains to you, the pharmacist, about the high price of the drug. The patient remarks that it cannot cost more than a few cents to make such a little tablet. “Who is making all the profit?” the patient queries. How would you address the patient’s concerns?
3. A pharmacist who is a member of a managed care formulary evaluation committee is evaluating whether to include on the formulary a newly marketed drug. The drug is more expensive than other drugs in its class and is rated by the FDA as type 5 and S. If you were the pharmacist, explain why you would or would not include the drug on the formulary.

4. As a pharmacist, you inform a patient that the patient’s copay will be $15 less if the patient gets the generic drug rather than the brand prescribed. The patient is concerned about quality and asks you whether generic drugs are as safe and effective as brand name drugs. How would you explain this to the patient?

5. A patient asks you, a pharmacist, whether OTC drugs are evaluated the same as prescription drugs for safety and efficacy. Provide an explanation to this patient.

6. Mentadine is an IND drug in phase 3. One of your terminally ill patients asks you if it is legally possible for her to get this drug. Respond to the patient’s inquiry.

7. A patient is prescribed a brand name drug. The patient asks if generics are available. Your research shows generics are available but unapproved by the FDA. You tell the patient this and the patient asks how it is legally possible that unapproved drugs can be sold and whether they are safe. Respond to the patient’s inquiry.

8. A physician calls you, a pharmacist, and tells you she suspects that a drug is causing a certain adverse reaction in some of her patients. She asks you if you have noticed anything similar and you report you have. She asks you if the adverse reaction should be reported, and if so, how and to whom?

9. A physician asks you, a pharmacist, what the difference is between class I, II, and III devices, and whether devices have to be approved by the FDA prior to marketing. Respond to the physician’s inquiry.

Drug Advertising and Promotion

Product advertising and promotion is essential to the commercial success of almost all products, and drug products are no exception. Because drugs are more dangerous than most products, however, and in the case of prescription drugs often require evaluation beyond the expertise of the consumer, the federal government has chosen to regulate the advertising and promotional activities of drug products more strictly than typical products. Congress has made two federal agencies responsible for the regulation of drug advertising. The FDA regulates prescription drug advertising under the FDCA (15 U.S.C. § 352(n)), whereas the FTC (usually in collaboration with the FDA) regulates nonprescription drug advertising under the Federal Trade Commission Act (15 U.S.C. § 45). Another federal law, the Lanham Trademark Act (15 U.S.C. § 1125), allows private parties a cause of action against false and misleading advertising. At the state level, most pharmacy practice acts prohibit pharmacists from false, misleading, or deceptive advertising. This chapter examines drug promotional activities by manufacturers, whereas Chapter 3 discusses promotional activities by pharmacies.

The First Amendment to the U.S. Constitution

Any government regulation of advertising and promotion creates legal controversy in light of the U.S. Constitution’s First Amendment guarantee of free speech. The U.S. Supreme Court has held that commercial speech (e.g., promotional activities by product sellers) falls under the First
Amendment, but has also recognized the need for government regulation of commercial activities, even when that regulation may have an incidental effect on speech in certain cases. Thus, government regulation must always walk the tightrope between protecting the public and violating free speech rights.

The Supreme Court has articulated the application of the First Amendment to commercial speech in the case of *Central Hudson Gas v. Public Service Commission*, 447 U.S. 557 (1980). When evaluating the governmental regulation of commercial speech, four factors must be considered:

1. The speech must not be misleading or related to an unlawful activity.
2. The government interest in the regulation must be substantial.
3. The regulation must directly advance the government interest asserted.
4. The restriction of speech cannot be more extensive than necessary to serve that interest.

There is no question that the FDA should be able to regulate drug product promotional activities under *Central Hudson*, but the issue becomes which activities, in what manner, and to what extent. For example, government regulation of company-sponsored educational symposia and company distribution of off-label use materials have faced First Amendment challenges. Any future governmental attempts to regulate activities such as direct-to-consumer advertising and Internet drug promotion must also pass test under the First Amendment.

**Prescription Drug Advertising: Manufacturer to Professionals**

Pharmaceutical manufacturers promote their products to health care professionals in several ways. Their methods range from advertising in professional journals to person-to-person contact through sales representatives. More controversial methods involve the sponsorship of medical symposia and the presentation of gifts and trips to health care professionals.

### Applicable Statute and Regulations

Section 502(n) of the FDCA, enacted in 1962, provides that a drug shall be deemed misbranded unless the manufacturer includes in all advertisements and other descriptive printed matter issued a “true statement” of

- The established name of the drug
- The formula, showing quantitatively each ingredient
- A “brief summary” of other information relating to side effects, contraindications, and effectiveness, required by regulation

Pursuant to this statute, the FDA has issued detailed regulations (21 C.F.R. Parts 200 and 201). The regulations mandate both the substance of the information that must be included (or not included) in the advertising and the manner in which it is presented (e.g., relative size of type, order of information).

The “true statement” requirement generally applies to all advertising, with certain exceptions. It does not apply to reminder advertising. “Reminder advertisements are those which call attention to the name of the drug product but do not include indications or dosage recommendations for use of the drug product” (21 C.F.R. § 201.1(e)(2)(i)). In addition to reminder advertisements, the regulations also exempt advertisements of bulk sale drugs (i.e., drugs intended to be processed, manufactured, or repackaged) and advertisements of prescription compounding drugs (i.e., drugs intended for use in compounding by pharmacists), as long as no safety or effectiveness claims are made.
A manufacturer has not met the true statement requirement if the advertising

- Is false or misleading
- Does not present a “fair balance” between side effects and contraindications information and effectiveness information
- Fails to reveal material facts

Fair balance essentially requires that the same scope, depth, and detail of information be presented for side effects and contraindications as for effectiveness.

The regulations list several examples of information in advertisements that are false, lacking in fair balance, or misleading (21 C.F.R. § 202.1(e)(6) and (7)). For example, an advertisement may not contain any representation or suggestion regarding a drug’s effectiveness or lack of side effects that has not been approved for use in the labeling, nor may an advertisement suggest that a particular drug is safer or more effective than another when this has not been demonstrated by substantial evidence. As another example, an advertisement is false, lacking in fair balance, or misleading if it contains favorable information from a study inadequate in its design, scope, or conduct.

Under the regulations, advertising includes advertisements in journals and other periodicals, advertisements in the broadcast media, and telephone communications. Brochures, booklets, mailing pieces, bulletins, calendars, price lists, references (e.g., the *Physicians’ Desk Reference*), and other such information disseminated by the manufacturer for use by health care professionals are considered labeling. Advertising and labeling must meet the same general standards; however, advertising need only contain a “brief summary” of the risks, whereas labeling must include the entire package insert.

The regulations somewhat modify the “true statement” requirements for advertising in broadcast media, such as radio and television. Because the brief summary requirement is really not that brief, manufacturers struggled to include all the required information in a short broadcast ad. As a result, prescription drug advertising in broadcast media need only include information about “major risks” instead of a full “brief summary,” provided that the manufacturer makes “adequate provision for the dissemination of the approved package labeling.” This alternative is called the “adequate provision” requirement, and is further described later in this chapter in the section discussing direct-to-consumer advertising.

**Journal Advertising**

Even a casual reader of medical journals cannot help but notice that many journal pages are devoted to pharmaceutical advertising. In 1991, the federal Office of the Inspector General (OIG) conducted a much publicized study to assess the accuracy, truthfulness, educational value, and quality of prescription drug advertisements in leading medical journals. Among other findings, the researchers concluded that most advertisements potentially violated FDA regulations and, if relied on, would lead to improper prescribing. The study confirmed and quantified what the FDA had suspected; in fact, the FDA had begun to step up its scrutiny and enforcement of prescription drug advertising before the study. Today the agency actively scrutinizes advertisements, and when necessary takes enforcement actions ranging from warning letters to lawsuits to requiring companies to run remedial advertisements and send corrective letters to health care professionals.

**Industry-Supported Educational Programs**

For several years, pharmaceutical manufacturers have sponsored and funded educational programs (usually for continuing education credit) for health care professionals. In pharmacy, this sponsorship is often important in the production of high-quality educational programs at a reasonable registration
fee for the pharmacist attendees. Concerns arise, however, when industry-supported programs are really product promotional activities disguised as educational programs.

A congressional investigation raised concerns about the objectivity of some manufacturer-sponsored educational programs and the inducements that some manufacturers were offering health care providers to attend (e.g., fees, free vacations). As a result of the congressional investigation, the FDA published a Draft Policy Statement on Industry-Supported Scientific and Educational Activities on November 27, 1992 (57 Fed. Reg. 56412-01), maintaining the agency’s traditional position that scientific and educational activities performed by or on behalf of drug manufacturers are subject to regulation under the FDCA. This policy statement was substantially modified and published as the Final Guidance on Industry-Supported Scientific and Educational Activities on December 3, 1997 (62 Fed. Reg. 64074).

The guidance attempts to distinguish between activities supported by companies that are otherwise independent from the promotional influence of the supporting company and those that are not. The FDA emphasized that it does not intend to regulate industry-supported programs that are independent and nonpromotional. The distinction becomes important because programs that are not deemed independent and nonpromotional are subject to labeling and advertising restrictions, meaning in part that off-label uses may not be discussed and the “true statement” requirements apply, including “fair balance.”

The guidance lists several factors the FDA will consider in evaluating whether an activity is independent. One factor is the degree of control the company has over the content of the program. Funding by a manufacturer for an educational program should be provided to a third party who conducts the program independently from the manufacturer. The manufacturer should not have a voice in determining program content in a truly independent program. Manufacturers commonly suggest the presenters, often academicians or clinical practitioners, to the third party, and this practice is completely permissible provided the content is objective and not influenced by the manufacturer. Other important factors include whether there was adequate disclosure during the program of the company’s funding support; the company’s relationship to the presenters; whether any unapproved uses will be discussed; whether the focus of the program is on educational content and free from commercial influence or bias; whether the audience was selected by the company, for example, as a reward to high prescribers, dispensers, or decision makers; and whether there are promotional activities, such as presentations or exhibits in the meeting room. In addition, although not required, a written agreement between the provider and the supporting company is encouraged to demonstrate that the sponsoring company has no involvement in the control or content of the symposia.

The guidance was challenged in Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51 (D.C. 1998), by a public interest group alleging that it violated the First Amendment (see the discussion in the case studies section). The court agreed that the guidance was overly restrictive and enjoined the FDA from prohibiting companies from being involved in the symposia content and discussing off-label uses as long as there is disclosure that the use is unapproved. The FDA appealed this decision in Washington Legal Foundation v. Henney, 202 F.3d 331 (C.A.D.C. 2000), arguing that a violation of the guidance is not illegal per se. Rather, continued the FDA, the guidance only serves as a “safe harbor,” informing manufacturers of conduct that would not be challenged by the agency. On this basis, the court found that no constitutional issue existed, vacating the district court’s decision that the guidance was unconstitutional. (Also see Washington Legal Foundation v. Henney, 36 F. Supp. 2d 418 (D.C. 1999).)

The Department of Health and Human Service’s Office of Inspector General voiced its opinion about manufacturer-funded educational activities in a document titled “OIG Compliance Program Guidance for Pharmaceutical Manufacturers” (68 Fed. Reg. 23731 (May 5, 2003)). In this voluntary
Compliance guidance, the OIG noted that manufacturers should ensure that they are not using educational activities to channel improper remuneration to healthcare providers in a position to generate business for the manufacturer. The OIG also stated that the manufacturer should have no control over the speaker or the content of the program. To do otherwise creates a risk that the manufacturer might violate the federal antikickback statute discussed in Chapter 6.

**Prescription Drug Advertising: Manufacturer to Consumer**

Manufacturer to consumer, known as direct-to-consumer (DTC), prescription drug advertising began in the early 1980s, breaking a tradition of advertising prescription drugs only to healthcare professionals. DTC advertising has become increasingly popular with drug manufacturers, touching off considerable controversy. Proponents contend that DTC advertising will benefit consumers by providing education, promoting awareness of potential health problems, improving compliance with drug therapies, and lowering drug prices. Pharmacists may benefit, according to the proponents, through increased prescription business and greater public recognition that they are the most knowledgeable and accessible source of additional prescription drug information. Opponents of DTC advertising contend that the practice will raise the cost of health care, create an inappropriate demand for medications and a demand for inappropriate medications, confuse patients, and jeopardize the physician-patient relationship.

There are no federal regulations that specifically address DTC advertising, meaning that essentially the advertising laws and regulations apply the same for DTC advertising, even though they were intended to regulate advertising to healthcare professionals, not consumers. Requiring the same criteria of a "true statement," a "brief summary," and "fair balance" creates problems as to whether these advertisements can be written in a manner that ordinary consumers can understand, especially because many manufacturers often use the same information regardless of the intended audience. In an effort to provide some direction and guidance to drug sponsors and ensure that consumers receive adequate communication of risk information, the FDA published a draft guidance in 1997 (notice at 62 Fed. Reg. 43171) and the final guidance in August 1999 (notice at 64 Fed. Reg. 43197). Of particular importance, the agency clarified what would satisfy the "adequate provision" requirement for DTC advertising through broadcast media. Advertisers may provide a summary of risks in audio and/or video form as long as there is "adequate provision" for the consumer to obtain full labeling information through a multifaceted approach from four sources: (1) a toll-free number, (2) an Internet webpage address, (3) referral to a print advertisement in a concurrently running print publication or by providing brochures in convenient outlets, and (4) referral to a health care provider. The FDA suggests that manufacturers should use all four sources of information. Although the regulations require that the approved product labeling (package insert) must be disseminated in connection with broadcast advertisements, the agency has instead asked manufacturers to consider translating the required information into language comprehensible to the general public.

Regarding DTC print advertising, the FDA announced in a 2004 draft guidance that it does not intend to hold manufacturers to the "brief summary" requirement, and in fact feels this level of information is not appropriate or useful for patients (U.S. Food and Drug Administration, 2004a). The draft guidance is intended to encourage manufacturers to present key risk information in consumer-friendly ways. The guidance emphasizes that DTC ads should list only the most serious and most common risks associated with the product. The FDA indicates two ways of doing this are by using a modification of FDA-approved patient labeling, such as patient package inserts, or MedGuides, which are discussed in Chapter 3. Or, at least until the FDA promulgates a regulation on this issue, manufacturers can include the information contained in the Highlights section of the package insert.
DTC advertising falls into one of two categories: nonproduct-specific or institutional advertising and product-specific advertising. The first type is educational in nature and does not mention the name of the product, only the name of the company. These advertisements generally inform the consumer about treatable diseases and that a physician can treat a particular condition with medications, and urge the consumer to see a physician. Because the advertisements do not mention the name of a product, they need not conform to FDA labeling and advertising requirements. Product-specific advertising is subject to the regulations, however. In an effort to encourage manufacturers to disseminate information about untreated and inadequately treated health conditions, the FDA published a draft guidance to help manufacturers distinguish between these “educational” type messages and “promotional” type messages (U.S. Food and Drug Administration, 2004b).

Just as the FDA scrutinizes advertising directed to health care professionals, it also evaluates advertising directed to consumers, and has taken enforcement actions. In 1991, for example, Ciba-Geigy was forced to discontinue its DTC advertising of Actigall, a drug used in an effort to dissolve certain kinds of gallstones, in response to FDA concerns. The FDA believed that the advertisements misled consumers by intimating that surgery was the only other choice of treatment when there are newer, less obtrusive forms of treatment available. At the same time, Ciba-Geigy agreed to cease using celebrities to promote its products.

In November 2006, the U.S. Government Accountability Office (GAO) issued a report titled “Prescription Drugs: Improvements Needed in FDA’s Oversight of Direct-to-Consumer Advertising” (www.gao.gov/cgi-bin/getrpt?GAO-07-54). As the title indicates, the GAO’s report criticized the FDA for several weaknesses. The GAO noted that DTC advertising had increased twice as fast from 1997 through 2005 as spending on promotion to physicians or on research and development, and the number of DTC materials the FTC received had doubled. The GAO reported that although the agency said it prioritizes all this material, the GAO could find no documented criteria for prioritization. Informal criteria being used by FDA reviewers is not systematically applied to all DTC materials. The GAO report further found that the FDA’s process for drafting and issuing violation letters takes longer, that the agency issues fewer letters, and that the effectiveness of the letters is limited.

Ultimately, the courts may have a significant influence as to the type of information a company must provide to consumers. The Supreme Court of New Jersey has held that when a manufacturer advertises its prescription product to consumers, it owes a legal duty to the consumer to properly warn of its product’s risks (Perez v. Wyeth Laboratories., Inc., 734 A.2d 1245 (N.J. 1999)). Historically, a company’s duty to warn of a prescription product’s risks is owed only to the health care professional, not the consumer. (This issue is discussed in Chapter 8.)

Promoting Prescription Drugs for Off-Label Uses

The promotion of off-label uses (also termed unapproved or unlabeled uses) most likely represents the FDA’s greatest concern within the area of advertising. The term off-label use refers to indications other than those approved by the FDA and thus that could not be included in the labeling. The FDA has historically been concerned that adverse health consequences can result if health care professionals and consumers are led to believe that a product is safe and effective for a use not approved by the agency. Thus, the agency has actively policed and basically prohibited any efforts by companies to disseminate off-label use information, even in the form of peer-reviewed journal articles, unless specifically requested by the health care practitioner (guidance published at 61 Fed. Reg. 52800 (1996)).
The FDAMA (§ 551 and § 552), however, relaxed FDA policy to allow companies to provide written information about off-label uses under certain conditions to:

- Health care practitioners
- Pharmacy benefit managers
- Health insurance plans
- Group health plans
- Governmental agencies

The written information must be in the form of unabridged peer-reviewed articles in scientific or medical journals or reference publications that have not been influenced by the company. There is some question as to whether the companies can legally provide the written information to pharmacists. The definition of health care practitioner generally might not include pharmacists. Section 561(1) defines a health care practitioner as a physician or other provider of health care who is licensed to prescribe under state law. Pharmacists lack prescriptive authority in nearly every state; however, in many states they have the authority to initiate or adjust drug therapies under collaborative practice agreements with physicians. Whether this collaborative authority would suffice to make a pharmacist a health care practitioner is unclear. In the FDA’s explanation of the final regulations implementing the off-label use laws (63 Fed. Reg. 64556 (1998)), the agency remarked that it was aware of this issue, but refused to modify the definition of health care practitioner to include pharmacists. The FDA did note that its definition of pharmacy benefit managers generally includes pharmacists, but the breadth of this inclusion is not clear.

The conditions for disseminating this information include that the company must (1) have filed an application for approval for the use; (2) submit to the agency 60 days before dissemination a copy of the information to be disseminated and any clinical trial information the company has; and (3) include with the disseminated information a disclosure that the use has not been approved, a copy of the official labeling for the product, any other products or treatments that have been approved for the use, the funding source for any studies relating to the use, and a bibliography of scientific publications regarding the use.

Some of these restrictions provided in the FDAMA had been ruled unconstitutional on First Amendment grounds by the Washington Legal Foundation v. Friedman and Washington Legal Foundation v. Henney cases mentioned previously and discussed in the case studies section. As stated previously, the court of appeals vacated the district court’s decisions after the FDA changed its position and asserted that the FDAMA provisions merely established a “safe harbor.” (Chapter 3 contains a discussion of the prescribing and dispensing of prescription drugs for off-label uses by health care practitioners.)

Nonprescription Drug Advertising by Manufacturers

As noted earlier, the FTC regulates nonprescription drug advertising under the Federal Trade Commission Act. The act allows the FTC to prohibit unfair methods of competition and unfair or deceptive acts or practices and to regulate advertising for foods, OTC drugs, and medical devices. The FTC cannot require companies to submit advertising to it for premarket approval but rather must act after the fact. The agency devotes top priority to advertisements in which the accuracy of the claims is difficult for consumers to verify; OTC drug advertisements often fall under this category. Moreover, the deceptive advertising claims of OTC products warrant priority on the basis that they can result in adverse health consequences and economic loss.
The FTC considers an advertisement deceptive when it contains a statement (or omission) of information that is likely to mislead reasonable consumers to their detriment. With this approach, the FTC need not prove that consumers were actually misled, only that they are likely to be misled. Advertising claims must have a reasonable basis. For example, if the advertisement states that the drug has been medically proven effective for a particular condition, the FTC expects the company to produce evidence to support the statement. The amount of verification that the FTC expects from the company depends on the type of advertising claim made, the type of product, the consequences of the false claim, the degree of reliance by consumers, and similar factors.

In *Porter & Dietsch, Inc. v. Federal Trade Commission*, 605 F.2d 294 (7th Cir.1979), the FTC challenged the advertising claims that the manufacturer made for X-11 diet tablets. The FTC contended that the advertisements were false and misleading because they proclaimed that users of the tablets can lose weight without changing their eating habits, that users will lose a significant amount of weight, and that X-11 contains a unique ingredient. The FTC also argued that the advertisements contained material omissions, including the information that persons with certain diseases should use X-11 tablets only as directed by a physician. The court decided in favor of the FTC because the company could produce no scientific basis for its claim of weight loss. As to the unique ingredient claim, the court agreed with the FTC that phenylpropanolamine had been in use for years and was hardly unique. Furthermore, the FTC admitted evidence showing that phenylpropanolamine could produce adverse effects in individuals with certain medical conditions, and the court agreed that this omission in the advertisements made them false and misleading.

In *Warner-Lambert Co. v. Federal Trade Commission*, 562 F.2d 749 (D.C. Cir. 1977), the FTC ordered Warner-Lambert to cease and desist misrepresenting the efficacy of Listerine mouthwash against the common cold. The company appealed the FTC’s findings in court, arguing that the FTC did not have the evidence to sustain a finding of false and misleading advertising. The court found for the FTC, however, after the agency introduced several facts into evidence including:

- The ingredients of Listerine are not present in sufficient quantities to have any therapeutic effect.
- It is impossible for Listerine to reach critical areas of the body in significant concentration through the process of gargling.
- Even if the active ingredients in Listerine could reach critical sites in significant quantities, they could not penetrate tissue cells and, thus, could not affect the viruses.
- Warner-Lambert’s clinical studies were unreliable.
- Even if Listerine kills millions of germs, as the advertisements claimed, it would be of no medical significance because these germs play no role in colds.

The FTC not only has the authority to issue cease-and-desist orders, but also can order companies to issue corrective advertising. In *Warner-Lambert*, the court upheld the agency’s order requiring the company to include this statement in every advertisement: “Listerine will not help prevent colds or sore throats or lessen their severity.” The court also supported the FTC’s order that this disclosure continue until the company had expended in Listerine advertising a sum equal to the average annual advertising budget for Listerine over a 10-year period, which amounted to approximately $10 million. The court viewed the corrective advertising as a necessary remedy for the erroneous consumer beliefs that the earlier advertising had fostered but cautioned that, because of the First Amendment, FTC restrictions may not be greater than necessary.
The FTC also has the authority to require advertisers to make affirmative disclosures when necessary to qualify certain statements (half truths) or to disclose certain adverse consequences of a drug. Often, the FTC collaborates with the FDA to determine whether there is a reasonable basis for a manufacturer’s claims regarding an OTC drug or whether it is permissible for a manufacturer to make a therapeutic claim about a food product. The FTC and FDA have an agreement through which the FTC regulates food advertising and the FDA regulates food labeling. The FTC allows manufacturers to make therapeutic claims about food products as long as the claims are properly qualified and there is a reasonable basis for the claim. Occasionally, this policy places the FTC at odds with the FDA, which may oppose the therapeutic claim on the label, contending that the claim makes the food a drug.

The Lanham Trademark Act

Frequently, one company objects to the advertising claims made by another company for a competing product. The objecting party may attempt to persuade the FTC to bring an action against its competitor, or it may bring an action itself under the Lanham Trademark Act, which prohibits the use of “any false description or representation, including words or symbols” in connection with the sale of any goods or services (15 U.S.C. § 1125).

The Lanham Act allows for a private cause of action and the recovery of monetary damages, as well as injunctive relief. It is not uncommon to find OTC drug manufacturers battling each other in court under the Lanham Act. For example, in American Home Products Corporation v. Johnson & Johnson, 654 F. Supp. 568 (S.D.N.Y. 1987), American Home Products, which markets Advil (ibuprofen), and Johnson & Johnson, which markets Tylenol (acetaminophen), sued each other for false advertising claims. Clearly annoyed at the two feuding companies, the judge commented that the lawsuit represents an endless war between two titans of the drug industry and involves more resources than small nations have used to fight for their very survival.

In the lawsuit, American Home Products claimed that Johnson & Johnson published false printed materials and broadcast false television commercials that unfavorably compared ibuprofen with acetaminophen. Johnson & Johnson, in turn, countersued American Home Products for false comparative advertising of Advil and two of its other OTC analgesic products, Anacin and Anacin-3. After hearing several expert witnesses and reviewing thousands of pages of exhibits and briefs, the court concluded that each party was guilty of misleading advertising, and it was too complex to determine the damages to each party caused by lost sales, profits, and goodwill.

Although plaintiffs usually bring an action under the Lanham Act for their own self-interest, the consumer benefits from these actions when they result in the removal of false and misleading advertising. The Lanham Act does not protect the consumer, however, if manufacturers conspire to advertise in their best interests rather than in the best interests of the consumer. Thus, the Federal Trade Commission Act has a more important role in protecting the consumer against false and misleading advertising.

**Study Scenarios and Questions**

1. You are the only pharmacist at a meeting with other health care professionals. A physician brings up the topic of direct-to-consumer drug ads on television and in magazines, lamenting that the ads are so seductive and misleading that some of his patients practically demand he prescribe the drugs for them. The physician and the other attendees wonder if the FDA regulates these ads. Explain to the group in attendance the requirements for drug advertising for broadcast and print media.
2. Xecor makes several drugs including Anxless, approved by the FDA for the treatment of anxiety. Recent studies sponsored by Xecor indicate that Anxless may be a promising treatment for hypertension. Dr. Mabel is a pharmacy professor whom Xecor approached to see if she would be willing to present hypertension C.E. programs. The company told Dr. Mabel it would pay her $2,000 per one-hour program, and the company would give her the slides to use. Dr. Mabel agreed, and Xecor sponsored a C.E. program at a local restaurant personally inviting the pharmacists. Most of the program was about the recent studies demonstrating how effective Anxless is for hypertension. The company also distributed articles to attendees discussing these studies. The FDA monitored the program and issued warning letters to Xecor and Mabel. Explain the legal and social policy arguments as to why this program might violate FDA guidelines and why it might not. What legal violation might Xecor and Mabel have committed?
Case Studies

Case 2–1: Nutrilab, Inc., et al. v. Schweiker, 713 F.2d 335 (7th Cir. 1983)

Issue: Is a product derived from a food source and promoted for the purpose of weight reduction by blocking the body’s digestion of starch a food or a drug?

Overview: In this case, the court confronted the issue of whether a product is really a food or a drug under the FDCA. Often courts are faced with ambiguous statutes and have to draw on their perception of legislative intent. Distinguishing a food from a drug has very significant regulatory implications. Food products are not subject to the premarket approval process as are drugs. Thus, in most cases if the FDA has objections over the promotion of a food product, the agency has the burden of proving its claim, during which time the product continues to be marketed. On the other hand, the FDA can withdraw a product from the market deemed to be a drug simply because it is an unapproved new drug. The agency would also have no difficulty establishing that the product is misbranded because the product’s label would not be in compliance with drug labeling requirements.

As the definition of drug indicates, the critical issue in distinguishing whether a product is a drug is the intended use of the product. In determining the intended use of a product, courts will consider evidence beyond the label and labeling. Thus, a court considers advertising from television, radio, magazines, the Internet, and so forth. Because the health, safety, and welfare of the public are often at stake in these cases, courts will often apply the definition of drug liberally in favor of the FDA.

As you read this case, consider the difference in the intent and meaning of Section 321(g)(1)(B) and Section 321(g)(1)(C) of the drug definition. Why are foods specifically excluded from being drugs under part C and not part B? How did the court ultimately define food for the purpose of part C? If this case were brought today, would the product be considered a dietary supplement under DSHEA?

The court first described the facts of the case:

Plaintiffs manufacture and market a product known as “starch blockers” which “block” the human body’s digestion of starch as an aid in controlling weight. On July 1, 1982, the Food and Drug Administration (“FDA”) classified starch blockers as “drugs” and requested that all such products be removed from the market until FDA approval was received. The next day plaintiffs filed two separate complaints in the district court seeking declaratory judgments that these products are foods under 21 U.S.C. 321(f) and not drugs under 21 U.S.C. 321(g). On October 5, 1982, the district court held that starch blockers were drugs under 21 U.S.C. 321(g), plaintiffs were permanently enjoined from manufacturing and distributing the products, and they were ordered to destroy existing inventories. The portion of the order requiring destruction of the products was stayed pending appeal.

The only issue on appeal is whether starch blockers are foods or drugs under the Federal Food, Drug, and Cosmetic Act. Starch blocker tablets and capsules consist of a protein which is extracted from a certain type of raw kidney bean. That particular protein functions as an alpha-amylase inhibitor; alpha-amylase is an enzyme produced by the body which is utilized in digesting starch. When starch blockers are ingested during a meal, the protein acts to prevent the alpha-amylase enzyme from acting, thus allowing the undigested starch to pass through the body and avoiding the calories that would be realized from its digestion.
Kidney beans, from which alpha-amylase inhibitor is derived, are dangerous if eaten raw. By August 1982, FDA had received 75 reports of adverse effects on people who had taken starch blockers, including complaints of gastrointestinal distress such as bloating, nausea, abdominal pain, constipation, and vomiting. Because plaintiffs consider starch blockers to be food, no testing as required to obtain FDA approval as a new drug has taken place. If starch blockers were drugs, the manufacturers would be required to file a new drug application pursuant to 21 U.S.C. 355 and remove the product from the marketplace until approved as a drug by the FDA.

After noting the facts and articulating the issue, the court proceeded to identify the relevant statutes, ascertain their meaning, and apply them to the facts of this case.

The statutory scheme under the Food, Drug, and Cosmetic Act is a complicated one. Section 321(g)(1) provides that the term "drug" means

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

The term "food" as defined in Section 321(f) means

(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.

Section 321(g)(1)(C) was added to the statute in 1938 to expand the definition of "drug." The amendment was necessary because certain articles intended by manufacturers to be used as drugs did not fit within the "disease" requirement of Section 321(g)(1)(B). Obesity in particular was not considered a disease. Thus "anti-fat remedies" marketed with claims of "slenderizing effects" had escaped regulation under the prior definition. The purpose of part C in Section 321(g)(1) was "to make possible the regulation of a great many products that have been found on the market that cannot be alleged to be treatments for diseased conditions."

It is well established that the definitions of food and drug are normally not mutually exclusive; an article that happens to be a food but is intended for use in the treatment of disease fits squarely within the drug definition in part B of Section 321(g)(1) and may be regulated as such. Under part C of the statutory drug definition, however, "articles (other than food)" are expressly excluded from the drug definition (as are devices) in Section 321(g)(1). In order to decide if starch blockers are drugs under Section 321(g)(1)(C), therefore, we must decide if they are foods within the meaning of the part C "other than food" parenthetical exception to Section 321(g)(1)(C). And in order to decide the meaning of "food" in that parenthetical exception, we must first decide the meaning of "food" in Section 321(f).

Congress defined "food" in Section 321(f) as "articles used as food." This definition is not too helpful, but it does emphasize that "food" is to be defined in terms of its function as food, rather than in terms of its source, biochemical composition, or ingestibility. Plaintiffs' argument that starch blockers are food because they are derived from food—kidney beans—is not convincing; if Congress intended food to mean articles derived from food it would have so specified. Indeed some articles that are derived from food are indisputably not food, such as caffeine and penicillin. In addition, all articles that are classed biochemically as proteins cannot be food either, because for example insulin, botulism toxin, human hair and influenza virus are proteins that are clearly not food.

If defining food in terms of its source or defining it in terms of its biochemical composition is clearly wrong, defining food as articles intended by the manufacturer to be used as food is problematic. When Congress
meant to define a drug in terms of its intended use, it explicitly incorporated that element into its statutory
definition. For example, Section 321(g)(1)(B) defines drugs as articles “intended for use” in, among other
things, the treatment of disease; Section 321(g)(1)(C) defines drugs as “articles (other than food) intended
to affect the structure or any function of the body of man or other animals.” The definition of food in Sec-
tion 321(f) omits any reference to intent. Further, a manufacturer cannot avoid the reach of the FDA by
claiming that a product which looks like food and smells like food is not food because it was not intended
for consumption.

Although it is easy to reject the proffered food definitions, it is difficult to arrive at a satisfactory one. In the
absence of clear cut Congressional guidance, it is best to rely on statutory language and common sense.
The statute evidently uses the word “food” in two different ways. The statutory definition of “food” in Sec-
tion 321(f) is a term of art and is clearly intended to be broader than the common sense definition of food,
because the statutory definition of “food” also includes chewing gum and food additives. Yet the statutory
definition of “food” also includes in Section 321(f)(1) the common sense definition of food. When the statute
defines “food” as “articles used for food,” it means that the statutory definition of “food” includes articles
used by people in the ordinary way most people use food—primarily for taste, aroma or nutritive value. To
hold as did the district court that articles used as food are articles used solely for taste, aroma, or nutritive
value is unduly restrictive since some products such as coffee or prune juice are undoubtedly food but may
be consumed on occasion for reasons other than taste, aroma, or nutritive value.

This double use of the word “food” in Section 321(f) makes it difficult to interpret the parenthetical “other
than food” exclusion in the Section 321(g)(1)(C) drug definition. As shown by that exclusion, Congress ob-
viously meant a drug to be something “other than food,” but was it referring to “food” as a term of art in the
statutory sense or to foods in their ordinary meaning? Because all such foods are “intended to affect the
structure or any function of the body of man or other animals” and would thus come within the part C drug
definition, presumably Congress meant to exclude common sense foods. Fortunately, it is not necessary to
decide this question here because starch blockers are not food in either sense. The tablets and pills at issue
are not consumed primarily for taste, aroma, or nutritive value under Section 321(f)(1); in fact, as noted ear-
erlier, they are taken for their ability to block the digestion of food and aid in weight loss. In addition, starch
blockers are not chewing gum under Section 321(f)(2) and are not components of food under Section
321(f)(3). To qualify as a drug under Section 321(g)(1)(C), the articles must not only be articles “other than
food,” but must also be “intended to affect the structure or any function of the body of man or other ani-
mals.” Starch blockers indisputably satisfy this requirement for they are intended to affect digestion in the
people who take them. Therefore, starch blockers are drugs under Section 321(g)(1)(C) of the Food, Drug,
and Cosmetic Act.

The court affirmed the decision of the district court, finding against the plaintiffs.

Notes on Nutrilab v. Schweiker:

1. Nutrilab points out the difference between part B of the drug definition and part C in that
part C broadens the term drug to include articles intended to affect the structure or function
of the body. If part C did not exist, the starch blockers would not likely be drugs because
they were not promoted for the prevention or treatment of a disease. Foods were excluded
under part C because all foods affect the function of the body. The question then becomes
whether a product is a food for the purposes of part C. This raises a corollary issue of
whether a product could be a food under the definition of food, but not be a food for the
purposes of part C. The court resolved the issue by concluding that the product was not a
food at all, and thus subject to part C. The court refused to expand its analysis to whether part C excludes any product defined as a food or just common sense foods.

2. Under DSHEA, structure/function claims about a dietary supplement made pursuant to the law are excluded from the drug definition. Would the starch blockers be a dietary supplement under DSHEA? They might, under the definition of dietary supplement, providing two conditions could be established: that they are a botanical and that they are meant to supplement the diet.

Case 2-2: United States v. Hiland, 909 F.2d 1114 (8th Cir. 1990)

Issue: Whether the defendants violated the FDCA by introducing a misbranded, unapproved, “new drug” into interstate commerce and whether they intended to mislead or defraud.

Overview: Like the Nutrilab case, this is a case in which a product becomes a drug on the basis of the intended use of the product by the sellers. Unlike Nutrilab, the defendants in this case committed a felony by allowing greed to blind their regard for public safety. Fortunately a case like Hiland does not occur often. Note that this case highlights the fact that individual officers can be held individually accountable for their actions under the FDCA. As you read this case, consider when a violation of the FDCA evolves from a misdemeanor to a felony.

Because of the many infants killed or seriously injured by the defendants’ vitamin E product, E-Ferol, this case is often mentioned as a reason why the FDA should have more, not less, authority over dietary supplements. As you read this case, ask yourself when does one intentionally violate the law as opposed to unintentionally violate the law, and what is the difference in consequences? About the time E-Ferol was being distributed, had the FDA allowed other unapproved drugs to be marketed? If so, on what basis, and why was this not a valid defense in this case? Also consider whether E-Ferol would be considered a dietary supplement today under DSHEA. Is there any way to prevent situations like this from occurring in the future? Are the penalties imposed on the defendants under the FDCA severe enough in light of the consequences of their crime?

The court related the facts of the case:

Carter-Glogau, located in Glendale, Arizona, was a manufacturer of generic injectable drugs. Carter was the corporation’s president and chief operating officer. OJF, located in Maryland Heights, Missouri, was a distributor of prescription pharmaceutical products, primarily generic drugs. Hiland was OJF’s president and Madison was its executive vice-president of operations. Almost all of the injectable drugs distributed by OJF were manufactured by Carter-Glogau. In most cases, the drugs manufactured by Carter-Glogau for OJF were generic copies of innovator drugs that were formulated by other companies and approved by the FDA.

In April 1982, one of Carter-Glogau’s customers wrote Carter to ask whether an intravenous form of vitamin E could be developed, noting that “[t]here must be a Hell of a market out there.” Carter expressed a reluctance to develop such a product. In his responses to the customer’s inquiry, he stated that the amount of polysorbates needed “may be detrimental,” and pointed out that “fat emulsions for IV use . . . are very tricky products and fraught with particular size problems.”

At the time, there was a significant need for an intravenous form of vitamin E to combat retrolental fibroplasia (RLF), a disease that causes impaired vision or permanent blindness in premature infants. Even though not approved by the FDA for this use, many neonatologists considered vitamin
E to be useful in reducing the incidence and severity of RLF. However, both the intramuscular and oral dosage forms currently available as nutritional supplements had drawbacks for administration to premature infants.

In August 1982, Madison wrote Carter to see if he could develop for OJF a high potency intravenous form of vitamin E for use in premature infants. He informed Carter that Hoffmann-LaRoche, a large pharmaceutical company, was testing an injectable vitamin E product for the treatment of RLF in an effort to obtain FDA approval of the product. Madison wrote that he was “afraid that when Roche gets their vitamin E approved, we will lose the business, unless you can come up with something.” Madison’s letter clearly indicated that the primary purpose of the product he was proposing would be to treat RLF, and stated, “We could always label it for vitamin E supplementation.” Hiland received a copy of this letter.

In his responses to Madison’s inquiries, Carter expressed serious safety concerns regarding the development of an intravenous vitamin E product, stating in part: “If we make some attempt to solubilize the vitamin E and use the wrong proportions and kill a few infants, we’d have some serious problems.” Carter was specifically concerned about developing such a product without proper clinical testing. He wrote Madison that: “The administration of this product intravenously in neonatals without appropriate clinical work concerning toxicity will undoubtedly lead to an exposure in terms of product liability which neither you nor we may wish to assume.”

Notwithstanding these safety concerns, after further dialogue with Madison, Carter proceeded to develop a high-potency intravenous vitamin E product called E-Ferol for OJF in the summer of 1983. Carter made the decisions as to the types and proportions of polysorbate the product would contain, admitting he did not know what levels were safe for premature infants. Moreover, neither he nor OJF did any testing to determine whether his formulation was safe and effective for premature infants. Later that summer Madison recommended to Hiland that E-Ferol be added to its product line for the treatment of RLF, and Hiland approved.

Carter and Madison then prepared the labeling for E-Ferol using the IM (nutrient supplement) label as the model, but adding a reference in the package insert about the product’s use in treating RLF. The labeling indicated the dosage at the level used to treat RLF.

In September 1983, OJF conducted a massive mailing campaign for E-Ferol, mailing out “Dear Doctor” letters accompanied by a brochure and package insert. The group targeted was involved in the treatment of RLF, but the promotional information did not indicate that E-Ferol had never been tested for safety and efficacy. At trial, the physicians and pharmacists testified that E-Ferol’s labeling led them to believe that the product was promoted to treat RLF in premature infants and that the product had been proven safe and effective. During the months that E-Ferol was on the market, OJF received various reports from hospitals and physicians of adverse reactions associated with the product, including infant deaths. After a report from a neonatologist in Spokane, Washington, in January 1984 regarding the death of three premature infants with excessively high levels of vitamin E, Hiland halted the distribution of E-Ferol and began an investigation. No effort was made to advise other users of the product of the reported deaths. Twelve days after the distribution of E-Ferol had been suspended, Hiland made the decision to resume all shipments of the product. The shipments continued until April 1984, despite further reports of infant deaths, at which time OJF recalled E-Ferol from the market.

A grand jury indicted Carter-Glogau, Carter, Hiland, Madison, and others. A trial was then begun resulting in the defendants being convicted of violating the FDCA on the basis of introducing into interstate commerce an unapproved “new drug” with the intent to defraud and mislead. The defendants were also convicted of misbranding E-Ferol on several counts including that the lab-
beling omitted material facts, failed to bear adequate directions for use, failed to bear adequate warn-
ings, and suggested uses dangerous to the health of premature infants. The basis of the fraud charge
was that the defendants intentionally represented the E-Ferol as safe and effective despite no test-
ing and continued to do so even after the adverse incident reports.

Madison and two other defendants plead guilty during the trial and were fined and given jail
sentences. Carter and Hiland were each sentenced to 9 years imprisonment, all but 6 months of which
was suspended, and fined $130,000. Carter-Glogau was also fined $130,000. Carter-Glogau, Carter,
and Hiland appealed.

Carter argues that his conviction on the new drug counts violated due process because (1) FDA policy ac-
tively led him to believe that E-Ferol could be marketed lawfully without a new drug approval, and (2) this
same policy was so vague and indefinite as to deprive him of fair warning that his conduct was illegal.

The court then proceeded to analyze the merits of the defendants’ arguments, first noting that the
FDCA prohibits the introduction of any new drug into interstate commerce without FDA approval
of safety and efficacy. Carter acknowledged this fact but argued that an FDA compliance policy
guide (CPG 7132c.02) specified that the FDA would defer enforcement action against unapproved
drugs marketed after 1962 that were identical or similar to existing pre-1962 drugs (DESI drugs) of
unresolved regulatory status, unless there was some reason to question the safety and efficacy of
the drug. The FDA applied this same policy (termed “ISR policy”) to drugs not included in the DESI
review, such as vitamin E products. Because of this ISR policy, Carter stated he was led to believe
that E-Ferol could be marketed without approval because it was similar to existing pre-1962 drugs.

The court, however, found no merit in the argument because Carter was allowed to introduce
extensive evidence on this issue at trial and the jury did not believe he relied on or was misled by
the policy. The court also found other reasons to reject Carter’s argument.

There are additional reasons why Carter’s argument must fail, aside from the jury’s rejection of his defense.
The FDA’s ISR policy did not purport to modify existing statutory requirements. The policy in no way sug-
gested that it was lawful under the FDCA to market a new drug without an approved NDA. It simply estab-
lished a set of enforcement priorities in an effort to best allocate limited FDA resources. Indeed, CPG 7132c.02
was adopted by the FDA after a federal court decision overturned its prior policy of permitting certain classes
of new drugs to be marketed without an approved NDA. CPG 7132c.02 expressly recognized that “all drugs
in the DESI review are ‘new drugs’ under the law,” and stated further:

It has been decided to reaffirm that all products marketed as drugs under the DESI program are new drugs
and therefore require an approved NDA or ANDA [abbreviated new drug application] for marketing. In view
of this reaffirmation of this policy, it is necessary that the Agency proceed to remove from the market any
current DESI-effective prescription products not subject of an approved NDA or ANDA, and to prevent in the
future the marketing of any such unapproved products.

Finally, we note that even if the ISR policy could somehow have been construed as making it legal to mar-
ket certain new drugs without an approved NDA, it certainly could not have been read as making such ac-
tion lawful when done with the intent to defraud or mislead.

Losing on this argument, Carter and Hiland claimed another defense.

Carter and Hiland contend that their convictions on the FDCA counts must be reversed because the district
court denied their request to instruct the jury that (1) knowledge that E-Ferol was an unapproved “new drug”
was an essential element of the new drug offense, and (2) knowledge that E-Ferol was “misbranded” was
an essential element of the misbranding offense. The court instructed the jury that the essential elements
of the new drug offense were (1) the defendants introduced E-Ferol into interstate commerce; (2) E-Ferol was an unapproved new drug; and (3) the defendants acted with the intent to defraud or mislead. The elements instruction for the misbranding offense was the same except that the court substituted the term “misbranded” for “unapproved new drug.”

Under Section 333(a)(1), neither knowledge nor intent is required for a misdemeanor violation. However, under Section 333(a)(2), there must be an intent to defraud or mislead for a felony violation. The defendants contended then that they could not violate Section 333(a)(2) unless it could be established that they had knowledge that E-Ferol was an unapproved drug and knowledge that E-Ferol was misbranded. The government, however, argued that the knowledge requirement of (a)(2) applies to the intent to defraud or mislead, not to the Section 331 violations. The court replied:

Given the fraud that the government alleged and sought to prove in the instant case, we think it is quite clear that Carter and Hiland could not have acted with the intent to defraud or mislead absent (1) knowledge that E-Ferol was a “drug” which was not approved by the FDA and had not been established as safe and effective for use in premature infants to treat RLF (i.e., was an unapproved “new drug”); and (2) knowledge that E-Ferol’s labeling contained misrepresentations and misleading omissions (i.e., was “misbranded”). Thus, we need not decide whether knowledge of the facts constituting the misdemeanor violation of 331 would be a separate and essential element of a 333(a)(2) violation in a case where the defendants could have acted with the intent to defraud or mislead without such knowledge. Our inquiry here is whether the court’s instructions were adequate to prevent the jury from convicting Carter and Hiland on the FDCA counts without finding that they had the knowledge necessary for the intent required by 333(a)(2).

Although not a model of clarity, we conclude that when viewed as a whole and in the context of the entire trial, the district court’s instructions fairly advised the jury that Carter and Hiland could not have acted with the intent to defraud or mislead without knowledge that E-Ferol was an unapproved new drug and misbranded.

Carter and Hiland also argued that the district court committed reversible error by giving a willful blindness instruction to the jury.

In essence, a willful blindness instruction “allows the jury to impute knowledge to [the defendant] of what should be obvious to him, if it found, beyond a reasonable doubt, a conscious purpose to avoid enlightenment.” As the First Circuit has noted, “[t]he purpose of the willful blindness theory is to impose criminal liability on people who, recognizing the likelihood of wrongdoing, nonetheless consciously refuse to take basic investigatory steps.”

We find no reversible error in the language used to instruct the jury on willful blindness. Viewed in the context of the entire jury charge, which included instructions on acts done knowingly, specific intent, and intent to defraud, the district court’s willful blindness instruction did not permit the jury to convict the defendants on the basis of negligent conduct. We reject Carter’s assertion that such an instruction must specifically state that a defendant has knowledge of a certain fact only if he is aware of a high probability of its existence, unless he actually believes that it does not exist.

Although the evidence in this regard was not overwhelming, taken as a whole it provided the jury with a reasonable basis for inferring that if Carter and Hiland did not actually know E-Ferol was dangerous and falsely labeled, it was only because they consciously chose to be ignorant of those facts. This inference could reasonably be drawn from the evidence concerning their responses to serious indications that E-Ferol was associated with the illness and deaths of premature infants.
Decision of the court: The court affirmed the lower court’s ruling against the defendants.

Notes on United States v. Hiland:

1. The FDCA imposes a strict liability (misdemeanor) requirement on product sellers, meaning that the mere introduction into interstate commerce of an unapproved or misbranded drug violates the law, regardless of whether the seller had any knowledge to this effect. The defendants tried to argue that intent to mislead or defraud (a criminal charge) cannot be established unless the government can prove they had knowledge that the product was an unapproved new drug and was misbranded. Usually in a fraud case, the prosecution must show knowledge. The government, however, argued that because knowledge to this effect is not required for the misdemeanor violation, it cannot be required for the fraud violation. The only elements required, argued the government, are that the defendants unknowingly committed the acts and had an intent to defraud. The court dodged the issue of whether knowledge must be proven or not by holding that the facts clearly showed that the defendants knew their product was promoted as a drug and was mislabeled.

2. The defendants contended that they thought they could market their product without approval on the basis of FDA policy. During the DESI review, the FDA had allowed generic drug manufacturers to continue marketing their products pending a determination of efficacy. This policy was voided, however, by a federal court. Even had the policy been valid, it would not have applied to E-Ferol, because it only applied to generics whose parent drug had been proven safe and effective. E-Ferol had no parent drug.

3. It is conceivable that if this case was brought today, the defendants would argue that the product is a dietary supplement, not a drug. This argument would not likely prevail, however. First, E-Ferol is intended for injection, and DSHEA defines a dietary supplement as one intended for ingestion. Second, the defendants clearly intended that the IV E-Ferol be used to treat RLF, a disease.


Issue: Whether the federal FDCA precludes terminally ill cancer patients from obtaining Laetrile, a drug not recognized as “safe and effective” within the meaning of 201(p)(1) of the act.

Overview: The FDA has historically been criticized for taking too long to approve new drugs for market; especially drugs intended for use in the terminally ill, where any delay is critical. In the 1970s and early 1980s, Laetrile gained considerable notoriety as a possible cure for cancer, despite little good scientific evidence as to its safety and efficacy. In fact, 17 states had legalized the use of Laetrile within their borders. The FDA, however, considered the product an unapproved drug and thus would not allow the interstate shipment of the drug. The plaintiffs in this case, terminally ill patients, argued that the FDCA does not prevent the availability of Laetrile for use for the terminally ill. A federal district court and court of appeals both agreed, although for different reasons, and the FDA appealed to the U.S. Supreme Court. This case raises some important policy issues. Should terminally ill patients have access to any medical treatment they want? In other words, what are we protecting terminally ill patients from by denying them access to the medical treatment of their choice? Would the public health still be protected if unapproved drugs for the terminally ill were legally available on the market but labeled with mandatory disclaimers that they were unapproved...
for safety and efficacy? Alternatively, should the drug approval process at least be expedited for drugs intended to treat life-threatening diseases? If the Supreme Court had agreed with the lower courts’ decisions, what effect might this have had on the commercial market for cancer treatments?

The Supreme Court first addressed the facts and applicable law:

Section 505 of the Federal Food, Drug, and Cosmetic Act prohibits interstate distribution of any “new drug” unless the Secretary of Health, Education, and Welfare approves an application supported by substantial evidence of the drug’s safety and effectiveness. As defined in 201(p)(1) of the Act, 21 U.S.C. 321(p)(1), the term “new drug” includes “[a]ny drug . . . not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling . . . .”

In 1975, terminally ill cancer patients and their spouses brought this action to enjoin the Government from interfering with the interstate shipment and sale of Laetrile, a drug not approved for distribution under the Act. Finding that Laetrile, in proper dosages, was nontoxic and effective, the District Court ordered the Government to permit limited purchases of the drug by one of the named plaintiffs. On appeal by the Government, the Court of Appeals for the Tenth Circuit did not disturb the injunction. However, it instructed the District Court to remand the case to the Food and Drug Administration for determination whether Laetrile was a “new drug” under 201(p)(1), and, if so, whether it was exempt from premarketing approval under either of the Act’s grandfather clauses.

After the administrative hearings order by the court, the FDA found that Laetrile was a new drug because it was not generally recognized among experts as safe and effective for its prescribed use. The agency further found that Laetrile was not exempt from premarketing approval under either the 1938 or 1962 grandfather provisions.

Reviewing the commissioner’s decision, the district court agreed that Laetrile was a new drug, but it ruled that Laetrile was exempt from the premarketing approval requirements, and also concluded that denying patients the right to use Laetrile infringed on their constitutionally protected privacy interests. The district court then granted an injunction, thus permitting the plaintiffs the use of Laetrile. The court of appeals approved the district court’s injunction against the FDA, but on different grounds. The appellate court found that the terms safety and effectiveness have no relevance to the terminally ill. These patients will die regardless of the treatment and thus there are no standards on which to judge the safety and efficacy for these patients. The court of appeals did, however, limit the availability of Laetrile to intravenous use only under physician supervision.

The Supreme Court then provided its analysis of the issue.

The Federal Food, Drug, and Cosmetic Act makes no special provision for drugs used to treat terminally ill patients. By its terms, 505 of the Act requires premarketing approval for “any new drug” unless it is intended solely for investigative use or is exempt under one of the Act’s grandfather provisions. And 201(p)(1) defines “new drug” to encompass “[a]ny drug . . . not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling.”

Nothing in the history of the 1938 Food, Drug, and Cosmetic Act, which first established procedures for review of drug safety, or of the 1962 Amendments, which added the current safety and effectiveness standards in 201(p)(1), suggests that Congress intended protection only for persons suffering from curable diseases. To the contrary, in deliberations preceding the 1938 Act, Congress expressed concern that individuals with fatal illnesses, such as cancer, should be shielded from fraudulent cures. Similarly, proponents of the 1962 Amendments to the Act, including Senator Kefauver, one of the bill’s sponsors, indicated an understanding that experimental drugs used to treat cancer “in its last stages” were within the ambit of the statute.
In implementing the statutory scheme, the FDA has never made exception for drugs used by the terminally ill. As this Court has often recognized, the construction of a statute by those charged with its administration is entitled to substantial deference.

In the Court of Appeals' view, an implied exemption from the Act was justified because the safety and effectiveness standards set forth in 201(p)(1) could have "no reasonable application" to terminally ill patients. We disagree. Under our constitutional framework, federal courts do not sit as councils of revision, empowered to rewrite legislation in accord with their own conceptions of prudent public policy. Only when a literal construction of a statute yields results so manifestly unreasonable that they could not fairly be attributed to congressional design will an exception to statutory language be judicially implied. Here, however, we have no license to depart from the plain language of the Act, for Congress could reasonably have intended to shield terminal patients from ineffectual or unsafe drugs.

A drug is effective within the meaning of 201(p)(1) if there is general recognition among experts, founded on substantial evidence, that the drug in fact produces the results claimed for it under prescribed conditions. Contrary to the Court of Appeals' apparent assumption, effectiveness does not necessarily denote capacity to cure. In the treatment of any illness, terminal or otherwise, a drug is effective if it fulfills, by objective indices, its sponsor's claims of prolonged life, improved physical condition, or reduced pain.

So too, the concept of safety under 201(p)(1) is not without meaning for terminal patients. Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use. For the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit. Indeed, the Court of Appeals implicitly acknowledged that safety considerations have relevance for terminal cancer patients by restricting authorized use of Laetrile to intravenous injections for persons under a doctor's supervision.

Moreover, there is a special sense in which the relationship between drug effectiveness and safety has meaning in the context of incurable illnesses. An otherwise harmless drug can be dangerous to any patient if it does not produce its purported therapeutic effect. But if an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible. For this reason, even before the 1962 Amendments incorporated an efficacy standard into new drug application procedures, the FDA considered effectiveness when reviewing the safety of drugs used to treat terminal illness. The FDA's practice also reflects the recognition, amply supported by expert medical testimony in this case, that with diseases such as cancer it is often impossible to identify a patient as terminally ill except in retrospect. Cancers vary considerably in behavior and in responsiveness to different forms of therapy. Even critically ill individuals may have unexpected remissions and may respond to conventional treatment. Thus, as the Commissioner concluded, to exempt from the Act drugs with no proved effectiveness in the treatment of cancer "would lead to needless deaths and suffering among patients characterized as "terminal" who could actually be helped by legitimate therapy."

The Court then noted that accepting the court of appeal's logic would have broad consequences. It bears emphasis that although the Court of Appeals' ruling was limited to Laetrile, its reasoning cannot be so readily confined. To accept the proposition that the safety and efficacy standards of the Act have no relevance for terminal patients is to deny the Commissioner's authority over all drugs, however toxic or ineffectual, for such individuals. If history is any guide, this new market would not be long overlooked. Since the turn of the century, resourceful entrepreneurs have advertised a wide variety of purportedly simple and painless cures for cancer, including liniments of turpentine, mustard, oil, eggs, and ammonia; peat moss; arrangements of colored flood lamps; pastes made from glycerin and limburger cheese; mineral tablets; and...
“Fountain of Youth” mixtures of spices, oil, and suet. In citing these examples, we do not, of course, intend to depreciate the sincerity of Laetrile’s current proponents, or to imply any opinion on whether that drug may ultimately prove safe and effective for cancer treatment. But this historical experience does suggest why Congress could reasonably have determined to protect the terminally ill, no less than other patients, from the vast range of self styled panaceas that inventive minds can devise.

The Supreme Court reversed the decision of the court of appeals, finding in favor of the FDA.

Notes on *United States v. Rutherford*:

1. The Supreme Court held that the requirements of the FDCA must be applied equally to all drugs, regardless of their intended use. At first impression it does seem bizarre that the government seeks to protect terminally ill patients from drugs not safe and effective when they are going to die anyway. The government’s restriction appears more reasonable considering that patients might forgo legitimate treatments, which might be effective, for worthless cures and that unscrupulous individuals would benefit at the expense of the helpless and desperate. Some First Amendment advocates would respond, however, that patients should have the right to choose any treatment they wish, provided that unapproved drugs are labeled with adequate warnings and disclaimers. A significant concern to the Court was the broad effect its decision would have on the commercial market, beyond Laetrile. If it agreed with the lower courts’ decisions, the Court was fearful it would give a green light to unscrupulous entrepreneurs to prey on desperate people.

2. The fact that the FDA opposed the plaintiffs in *Rutherford* does not imply that the FDA was unsympathetic to the plights of the terminally ill. The FDA has continuously studied the issue of how the approval system could better accommodate the needs of those with life-threatening illness and yet still protect them from products that might worsen their situation and from quackery. As discussed earlier, the agency did enact regulations to allow the use of investigational drugs and expedite the approval of drugs for serious and life-threatening diseases, and these regulations were ultimately codified in the FDAMA.

3. Although the plaintiffs raised the constitutional issue that their right of privacy was violated, both the court of appeals and the Supreme Court did not address it. This is common because courts will not address complex constitutional issues if the controversy can be decided on other grounds.


**Issue:** Whether the FDA’s guidance publications restricting the use of textbook and journal reprints and educational seminars promoting off-label uses violate the First Amendment.

**Overview:** As noted in the advertising and promotions section of this chapter, the First Amendment is a significant factor in any governmental attempt to regulate in this area. At issue in this case is the constitutionality of two FDA policy guidances, one of which establishes restrictions for drug manufacturers disseminating textbooks and journal articles related to off-label uses and the other of which restricts a company from discussing the off-label uses of its drug at educational symposia that it sponsors. (Refer to the advertising section in this chapter for a discussion of the guidance poli-
cies.) Because the FDAMA was enacted after the guidance regulating the dissemination of written materials was published, supplanting the guidance, the constitutionality of the FDAMA provisions became an issue in a subsequent decision discussed in the notes after the case. The plaintiffs in this case contend that the guidance policies are too restrictive and thus violate the First Amendment.

As you read this case, ask: What is the primary reason why manufacturers want to notify health care providers of off-label uses? Has the FDA gone too far in its restrictions of discussing and disseminating off-label uses, or are the restrictions really necessary to protect the public? What alternatives did the court suggest that would be less restrictive than the FDA’s off-label use policy, yet still protect the public? Does this case mean that the FDA cannot in any way restrict manufacturer promotion of off-label uses? Although this decision was appealed and the constitutional issues dismissed, this decision raises valid concerns and highlights the delicate relationship between government regulation and First Amendment rights.

The court started its analysis with a discussion of the facts.

Plaintiff Washington Legal Foundation (“WLF”) is a nonprofit public interest law and policy center that defends “the rights of individuals and businesses to go about their affairs without undue influence from government regulators.” In this action, WLF seeks to enjoin the Food and Drug Administration, (“FDA”) and the Department of Health and Human Services (“HHS”) from enforcing policies restricting certain forms of manufacturer promotion of off-label uses for FDA-approved drugs and devices. The policies at issue—expressed through Guidance Documents—concern manufacturer distribution of reprints of medical textbooks and peer-reviewed journal articles (“enduring materials”), and manufacturer involvement in continuing medical education seminars and symposia (“CME”).

Plaintiff seeks a declaratory judgment that the FDA policies expressed in the Guidance Documents violate the rights of its members under the First Amendment of the Constitution. It further requests that the court enter preliminary and permanent injunctions against defendants, preventing them from enforcing, relying upon, or otherwise giving effect to the Guidance Documents.

The court then reviewed the regulatory framework for drug approval, finding that the FDCA clearly proscribes the labeling of off-label uses by manufacturers. The court noted that 21 U.S.C. § 321(p) makes it clear that drugs must be proven safe and effective for “use under the conditions prescribed,” meaning that a drug must have FDA approval for each use. Otherwise the use is unapproved and considered to be off-label. Manufacturer promotion of off-label uses constitutes misbranding under 21 U.S.C. § 352. The court, however, also noted a significant discrepancy between the regulatory framework and medical practice.

Central to this litigation is that what a manufacturer may lawfully claim that a drug does under the statutory and regulatory scheme, and what a physician may prescribe a drug for, do not match. Once a drug has been approved by the FDA for marketing for any use, the actual prescription choices regarding those drugs are left to the discretion of the physician. A physician may prescribe an approved drug for any medical condition, irrespective of whether FDA has determined that the drug is safe and effective with respect to that illness. The FDA contends that it accepts the practice of off-label use by physicians as part of its enforcement discretion, though it appears to be an open question as to whether the FDA could currently regulate this aspect of the practice of medicine if it wished to do so.

In light of this discrepancy, the court considered the merits of off-label use, noting that it is an accepted aspect of a physician’s prescribing regimen and that even the FDA has acknowledged that off-label use constitutes good medical practice in appropriate situations. The court also noted that the FDA has stated that physicians need current and reliable information about off-label uses, but that off-label prescribing can pose problems to the public.
The plaintiffs did not disagree with the FDA completely but argued that the guidance documents are too restrictive under the First Amendment, because one guidance prohibits entirely the discussion of off-label uses at company-sponsored promotional symposia and the other prohibits the unsolicited distribution of articles and texts addressing off-label uses. (The court noted that the FDAMA subsequently replaced this guidance, permitting distribution provided that the manufacturer submits an application to have the new use approved by the FDA. Nonetheless, the court included this guidance in its ruling.) The court then launched its First Amendment analysis of the guidance restrictions starting with the issue of how to classify the speech being regulated.

Plaintiff argues that it is scientific and academic speech, which is entitled to the highest level of First Amendment protection. Defendants challenge this assertion by first making a somewhat difficult to discern argument that the Guidance Documents regulate conduct. A closer examination demonstrates that what the FDA is actually contending is that because the federal government has the broad power to regulate the pharmaceutical industry, the Guidance are incidental encroachments upon speech and entirely compatible with the First Amendment. In the alternative, FDA claims that the Guidance Documents at most regulate commercial speech, which is subject to a more relaxed inquiry than core First Amendment speech.

The court had no difficulty concluding that the guidance documents regulate speech, not conduct. The conduct, stated the court, is the off-label prescribing by physicians, but the guidance documents regulate the off-label dissemination activities by the manufacturers, which encourage the conduct, and are speech. The issue of whether the speech is pure speech or commercial speech gave the court more difficulty.

The resolution of this question is not an easy one, as the communications present one of those “complex mixtures of commercial and non-commercial elements.” Typical “commercial speech” is authored and/or uttered directly by the commercial entity that wishes to financially benefit from the message. A purveyor of goods or services makes claim about his products in order to induce a purchase. In this instance, by contrast, the speech that the manufacturers wish to “communicate” is the speech of others—the work product of scientists, physicians and other academics.

Nonetheless, the court found that the purpose of the manufacturer’s dissemination of pure speech by others is to influence prescribers and in turn increase sales. Therefore, the court concluded the speech is commercial. The court then proceeded to analyze whether the government regulation of this commercial speech is constitutional under Central Hudson’s four-prong test (see summary of Hudson in this chapter).

_Hudson’s_ first prong is that the speech must be neither unlawful nor inherently misleading. Regarding the unlawful issue, the court found it could not be unlawful because the speech promotes the conduct of prescribing drugs for off-label uses, a lawful activity. As for the inherently misleading component, the court noted that the speech must be “more likely to deceive the public than to inform it,” stating:

In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.

To categorize the speech at issue here as “inherently misleading” is particularly unsupportable when one considers all the controls available to FDA to ensure that the information manufacturers wish to distribute is scientifically reliable, and therefore less likely to even be “potentially misleading.”

The court listed the controls that the FDA retains over off-label use promotion after its decision, which would allow the FDA to:
• Require a disclaimer that the uses have not been approved by the FDA
• Require that reprinted articles come from a bona fide peer-review journal
• Require that textbook reprints be published by a “bona fide independent publisher”
• Require that for CME seminars and symposia, the sponsor must be an “independent program provider”
• Require manufacturers that sponsor or provide financial support for the dissemination of articles or reference textbooks or for seminars and symposia to disclose (a) their interest in the product promoted and (b) the fact that the use discussed has not been approved by the FDA
• Enforce any rules, regulations, guidance, statutes, or other provisions of law that sanction the dissemination or redistribution of material that is false or misleading

Finding that the manufacturers’ speech is neither unlawful nor inherently misleading, the court addressed the second prong, whether the government’s interest is substantial. The court noted that the government has two interests: one, that physicians receive accurate and unbiased information; and two, that manufacturers receive ample incentive to get the unapproved uses approved. The first reason, stated the court, is not legitimate. The government cannot assume paternalistically that the public will use truthful, nonmisleading information unwisely, especially in this situation, where the public is physicians who possess the knowledge and sophistication to make informed choices and are capable of evaluating the materials distributed to them. As for the second reason, the court did find that the government has a substantial interest in compelling manufacturers to seek approval for off-label uses because the FDCA requires it.

The court then addressed the third prong of the Hudson test, whether the guidance documents advance a substantial government interest “in a direct and material way” by requiring manufacturers to submit supplemental applications to obtain approval for new uses. The court held that they did, noting that manufacturers would otherwise avoid submitting approved drugs for subsequent approval because of the time and cost involved and the fact that the drugs were already on the market.

The court lastly analyzed the fourth prong, whether the guidance documents restrict more extensively than is necessary, concluding that the restrictions were more extensive than necessary to achieve the government’s substantial interest of encouraging manufacturers to get new uses approved.

This determination is based in large part upon the fact that there exist less burdensome alternatives to this restriction on commercial speech. The most obvious alternative is full, complete, and unambiguous disclosure by the manufacturer. Full disclosure not only addresses all of the concerns advanced by the FDA, but addresses them more effectively. It is less restrictive on speech, while at the same time deals more precisely with the concerns of the FDA and Congress.

Full disclosure, concluded the court, will assuage concerns that the manufacturer’s promotions are inherently misleading because physicians would know that the product has not been approved for the use promoted. In addition, stated the court, manufacturers would still have adequate incentives to obtain approval for new uses for several reasons:

• They are proscribed from producing and distributing marketing materials for off-label use.
• They cannot be involved in seminars unless conducted by an independent program provider.
• They cannot initiate person-to-person contact with a physician about the off-label use.
• They cannot advertise off-label uses to consumers.
Also, noted the court, because of malpractice concerns, FDA approval is important to physicians. The court granted the plaintiff's motion, enjoining the FDA from restricting any company from disseminating to health care professionals peer-reviewed published articles or reference textbooks that discuss off-label uses. The agency also may not prevent companies from suggesting content or speakers to independent educational symposia regarding off-label uses. The FDA is permitted to impose the six controls previously stated.

Notes on *Washington Legal Foundation v. Friedman*:

1. In applying the *Hudson* test to this case, the judge found that the company's dissemination of off-label use information was not unlawful because the speech is intended to promote the activity of prescribing drugs for off-label use, which is lawful. Could it not be equally valid that the speech is intended by the manufacturers to further the activity of marketing drugs for unapproved uses, an illegal use? Should the decision turn on the conduct of the physicians or the conduct of the manufacturers?

2. After the decision, the FDA filed a motion with the court to confine the injunction to the policy guidance only and not to the FDAMA, which became effective after the decision. The WLF challenged this motion and the court found for the WLF, stating that the injunction applied to the pertinent policies contained in the FDAMA, not just the guidance documents (*Washington Legal Foundation v. Friedman*, 36 F. Supp. 2d 16 (D.C. 1999)). Otherwise, stated the court, the FDAMA would render its decision meaningless. The court stopped short of declaring any specific portion of the FDAMA unconstitutional, however, until after the parties submitted briefs and adjudicated the matter.

3. The matter was then adjudicated in *Washington Legal Foundation v. Henney*, 36 F. Supp. 2d 418 (D.C. 1999), where the judge, after reviewing the FDAMA's restrictions on manufacturer dissemination of peer-reviewed articles and texts, declared that insofar as the restrictions perpetuated policies previously determined unconstitutional, those portions of the FDAMA must also be unconstitutional. In particular, the court found disfavor with the FDAMA requirement that off-label use information could be disseminated only if a supplemental application has been submitted for approval. Stated the court, “The supplemental application requirement amounts to a kind of constitutional blackmail—comply with the statute or sacrifice your First Amendment rights. It should go without saying that this tactic cannot survive judicial scrutiny.” The court continued by noting that the supplemental application requirement is unnecessary in light of the numerous other incentives that exist for manufacturers to seek approval for off-label uses as determined in the *Friedman* decision.

4. The FDA appealed the *Friedman* and *Henney* decisions in *WLF v. Henney*, No. 99 5304 (D.C. 2000), insofar as the decisions declared unconstitutional the CME guidance and the FDAMA provisions regulating the dissemination of articles and textbooks. (The FDA conceded that the FDAMA superseded the guidances related to regulating the dissemination of articles.) The appellate court was prepared to consider the constitutional issue, when in a surprise move, the FDA asserted that it had no authority to regulate manufacturer speech. Instead, argued the agency, the requirements contained in the FDAMA and CME guidance only establish a “safe harbor,” ensuring that certain forms of conduct would not be used against manufacturers. Thus, continued the FDA, neither the FDAMA nor CME guidance authorize the FDA to prohibit or to sanction speech. If a company wants to disseminate off-label use information in violation of the FDAMA or CME guidance, that would not be a per se violation of the law and would not trigger agency sanction. The FDA, however, would retain
the right to use the conduct as evidence in a misbranding or intended use enforcement action. In light of this “new” position by the FDA, both parties then agreed that the FDAMA and CME guidance do not facially violate the First Amendment. In light of this agreement, the court found a constitutional controversy no longer existed. It therefore refused to consider the merits of the district court’s decision as requested by WLF, dismissing the FDA’s appeal and vacating the district court’s decisions holding the FDAMA and CME guidance unconstitutional.