CHAPTER 2

Federal Regulation of Medications: Development, Production, and Marketing

CHAPTER OBJECTIVES

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

- Identify the significant historical events that have shaped the current U.S. federal Food, Drug, and Cosmetic Act (FDCA).
- Describe the organization of the U.S. Food and Drug Administration (FDA).
- 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 (OTC) drugs.
- Understand the issues and procedures pertaining to new drug approval.
- Describe why there are unapproved drugs on the market.
- Understand the regulatory system related to drugs intended to treat serious and life-threatening diseases.
- Distinguish biologics from other FDCA products.
- Describe the MedWatch program.
- Understand the process by which medical devices are regulated under the FDCA.
- Describe the legal requirements for manufacturers that advertise prescription drugs to healthcare 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, devices, and cosmetics introduced into interstate commerce. The intent of the law is to protect consumers from adulterated or misbranded foods, drugs, cosmetics, or devices. Under the FDCA, 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 U.S. 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. In many sections, 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 authors.

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 United States in the 1800s against the adulteration of foods and drugs were led by two factors: (1) advances in analytical chemistry and microscope technology and (2) 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 7 years over certain periods of time in Boston and New York, in part because of adulterated drugs and foods (Hyman, 2002, Chapter 2).

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

Pure Food and Drug Act of 1906

At the turn of the 20th 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. However, it fell short of providing the protection that Congress intended, 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, purity). Some manufacturers, fearing a violation of the labeling provision, simply omitted information from the label because the Pure Food and Drug Act did not require the label to list the ingredients, include directions for use, or provide warnings. Moreover, the Pure Food and Drug 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 Pure Food and Drug 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 mounting 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" antiinfective sulfa drugs marketed. A manufacturer who sought to produce the drug in an elixir form deemed diethylene glycol the best solvent. (Diethylene glycol is used today 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 must 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 of 1997 (FDAMA) 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. The defendant pharmacist contended that federal law did not apply to his acts because his acts affected only intrastate transactions. The U.S. Supreme Court, 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 Durham-Humphrey Amendment established two classes of drugs—prescription and OTC—and provided that the labels of prescription drugs need not contain "adequate directions for use" as long as they contain the legend, "Caution: Federal law prohibits dispensing without prescription." Today, the federal legend is abbreviated as "Rx only." 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.

Food Additives Amendment of 1958

After several years of hearings, Congress amended the FDCA to require that components added to food products 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.

The Kefauver-Harris Amendment, also called the Drug Efficacy Amendment (76 Stat. 780), strengthened the new drug approval process by requiring that drugs not only be proved safe but also effective. The efficacy requirement was made retroactive to all drugs marketed between 1938 and 1962. The Kefauver-Harris 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 it 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 (MDA) (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 less than 200,000 persons in the United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the US a drug for such disease or condition will be recovered from sales in the US of such drug). Between the act's passage and 2022, the FDA has designated 6,349 orphan products. Because the number of applications for orphan drug designations increased steadily since 2012, a backlog of requests mounted at the agency. This prompted the FDA to launch the Orphan Drug Modernization Plan on June 29, 2017, with one of its intended goals to eliminate the backlog. The database for orphan drugs can be accessed and searched at https://www.accessdata.fda.gov/scripts/opdlisting/oopd. The FDA enacted a final rule on June 12, 2013, clarifying various provisions in the Act (78 Fed. Reg. 35117; 21 CFR part 316).

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 (DPC/PTRA) (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 (PDMA) (P.L. 100-293) in 1987 in response to the growing alarm that a secondary or diversionary distribution system for prescription drugs was threatening the public's 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 healthcare entities from reselling their pharmaceutical purchases to other businesses and requires the state licensing of drug wholesalers.

Safe Medical Devices Act of 1990

The Safe Medical Devices Act further strengthened the MDA Act of 1976, giving the FDA additional authority, especially related to postmarketing requirements and premarket notification and approval, while expediting the premarket device approval process.

The Generic Drug Enforcement Act of 1992

The Generic Drug Enforcement 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 seeking NDAs 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 expedite the NDA reviews. In the FDA's 2021 Fiscal Year, the FDA had net collections of $1.153 billion in prescription drug user fees. The PDUFA Financial Reports can be accessed at https://www.fda.gov/about-fda/user-fee-financial-reports/pdufa-financial-reports. PDUFA must be reauthorized every 5 years, and on September 30, 2022, the President signed into law the FDA User Fee Reauthorization Act of 2022 (PDUFA VII). This is the sixth reauthorization of PDUFA and will continue until 2027.

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 gave too much authority to 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 (P.L. 105-115).

Building on the PDUFA, 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, healthcare 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 repository 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 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 FDAMA 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.

Medical Device User Fee and Modernization Act of 2002

Similar to PDUFA, the Medical Device User Fee and Modernization Act (MDUFMA) established user fee requirements for premarket reviews of medical

devices (P.L. No. 107-250). It also established performance goals for many types of premarket reviews, inspections that can be conducted at establishments by accredited third parties, and new regulatory requirements for reprocessed single-use devices. As with PDUFA, the user fee requirement must be renewed by Congress every 5 years.

Food and Drug Administration Amendments Act of 2007

Congress passed the Food and Drug Administration Amendments Act (FDAAA) in September of 2007 (P.L. No. 110-85), reauthorizing and amending many drug and medical device provisions that were set to expire, while providing the FDA with new funding and significantly more authority over drug safety. The FDAAA allows the FDA broader use of the fees generated from PDUFA, while substantially increasing the fees. In response to postmarket problems with certain drug products such as Vioxx, which had to be removed from the market because of safety concerns, the law provides the FDA with significantly enhanced responsibilities and authorization to regulate drug safety, including the authority to mandate labeling changes related to safety, require clinical trial data reporting and registries, require postmarket clinical studies to assess risks, and require companies to implement risk evaluation and mitigation strategies (REMS) when necessary.

Patient Protection and Affordable Care Act of 2010

The Patient Protection and Affordable Care Act (ACA), enacted in March 2010, provided sweeping changes throughout the entire healthcare system (P.L. No. 111-148). The U.S. Supreme Court has ruled that most of the provisions in the act are constitutional (*National Federation of Independent Business v. Sebelius*, 132 S. Ct. 2566 (June 28, 2012)). Although the ACA added healthcare law far beyond the scope of the FDCA, it bears mentioning in this section on regulatory history because it added provisions to the FDCA and directly and indirectly affected other laws related to pharmacy practice.

FDA Safety and Innovation Act of 2012

The primary purpose of the FDA Safety and Innovation Act (FDASIA) (P.L. No. 112-144) was to reauthorize PDUFA, allowing the FDA to continue to collect user fees from manufacturers seeking NDAs or medical device approvals. In addition, it adds new user fees for generic drugs (Generic Drug User Fee Act [GDUFA]) and biosimilars (Biosimilar User Fee Act [BsUFA]). The purpose of imposing fees on these manufacturers is to increase resources of the FDA in order to speed the generic drug and biosimilar approval process. As with PDUFA, Congress must reauthorize these laws every 5 years. The law also contains several other provisions directed at reducing drug counterfeiting, blocking the import of adulterated products, detecting and reducing drug shortages, and enhancing the exchange of prescription drug diversion information across state lines. Additionally, the law enables the FDA to inspect foreign drug manufacturers more regularly and requires the agency to target problematic manufacturing sites, whether in the United States or not. Congress anticipates that the law will help bring critical drugs and medical devices to market faster and enhance the availability of generic drugs.

Drug Quality and Security Act of 2013

Title I of the Drug Quality and Security Act (DQSA) (P.L. No. 113-54), called the Compounding Quality Act, clarifies and strengthens FDA oversight over pharmacies engaged in the large-scale compounding and shipping of sterile products to other licensed entities. This change in the FDCA occurred in response to a meningitis outbreak that killed over 60 people and injured hundreds of others, and was caused by contaminated drugs compounded by the New England Compounding Center, a Massachusetts pharmacy. Entities compounding sterile products (known as outsourcing facilities under the law) may voluntarily register with the FDA and must comply with Current Good Manufacturing Practices (CGMP). The law also removed uncertainty regarding when a product compounded by a pharmacy is exempt from the CGMP, labeling, and new drug approval process. Title II of this law, known as the Drug Supply Chain Security Act, adds "track and trace" requirements for all entities in the chain of distribution of pharmaceutical products. By 2015, manufacturers were required to provide transaction information to purchasers, who, in turn, had to provide transaction information to subsequent purchasers (e.g., wholesalers and pharmacies). The law also mandated an electronic,

interoperable product tracing system by 2023, strengthened wholesaler and third-party logistics licensure requirements, and required manufacturers to serialize drugs by 2018 (which the FDA extended from the original 2017 deadline).

The 21st Century Cures Act of 2016

The 21st Century Cures Act (Cures Act) was passed in 2016, in large part to streamline and add flexibility and innovation to the drug development and approval process, primarily by creating new clinical trial design options and by accelerating the pathways to market for drugs intended to treat certain serious or life-threatening diseases (P.L 114-255). The law authorized $500 million over 9 years to the FDA to carry out specific medical product development innovation activities. Opponents to the Cures Act fear that speeding drug approval in this manner amounts to shortcuts that will endanger public safety. The law also provided billions of dollars of additional funding to the National Institutes of Health (NIH), to allow current medical research efforts to progress and spur new research. Increased funding was also expected to be made available to address mental health and substance abuse issues.

FDA Reauthorization Act of 2017

The FDA Reauthorization Act (FDARA) (P.L. 115-52) of 2017 reauthorized the user fee programs established by PDUFA for the fifth time, the MDUFA for the third time, and the GDUFA and the BsUFA for the first time. It also enhanced the goals of the Cures Act in several ways and created a new category of OTC hearing aids. Since the 2017 reauthorization, the user fee programs were again reauthorized in 2022 and will continue until 2027 (see section *Prescription Drug User Fee Act of 1992)*.

Food and Drug Omnibus Reform Act

The Food and Drug Omnibus Reform Act (FDORA) was passed on December 29, 2022. It encourages clinical trial diversity, provides reforms to the FDA accelerated approval process, updates the regulatory process for cosmetics and enhances the FDA's oversight of infant formulas.

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 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 not only 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 available drugs 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 (P.L. 101-508), one of the later major federal drug laws, focuses on informed decisions by patients rather than on decisions by government or healthcare providers on behalf of patients. It is also perhaps no coincidence that the past couple of decades has witnessed an unprecedented number of drugs that were switched from prescription status to over-the-counter (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 healthcare decisions rather than passively accepting therapies decided on by others.

Take-Away Points

- Although the first law directed at protecting the public from food and drugs was enacted in 1906, the nucleus of the FDCA as we know it today was enacted in 1938. The 1938 law required that drug products not already on the market could not be marketed until proven safe and required drug labeling to contain adequate directions for use and warnings.
- The Durham-Humphrey Amendment established two classes of drugs: prescription and OTC.
- The Kefauver-Harris Amendment, passed in 1962, added the efficacy requirement for drug products, which was made retroactive to 1938. Drug products marketed prior to 1938 remained exempted.
- The Orphan Drug Act of 1983 provides incentives for manufacturers to develop and market drugs and biologicals for the treatment of rare diseases or conditions.
- The DPC/PTRA of 1984 facilitated the approval process of generic drugs while affording patent extensions to innovator drug products.
- The PDMA of 1987 established requirements for prescription drug sample distributions and prohibits the resale of pharmaceuticals by hospitals and other healthcare entities to other businesses.
- The PDUFA of 1992 requires manufacturers to pay application fees for NDAs.
- The DSHEA of 1984 created the class of products called dietary supplements and required the FDA to regulate these products more as foods than as drugs.
- The FDAMA, passed in 1997, streamlined regulatory procedures to expedite the availability of drugs and devices and created a fast-track process for drugs intended for serious or life-threatening diseases.
- The FDAAA, passed in 2007, provided the FDA with significantly enhanced authority to regulate drug safety, including requiring REMS when necessary.
- The FDASIA of 2012 adds user fees for generic drugs and biosimilars, among several other provisions.
- The DQSA of 2013 clarified the law related to pharmacy compounding, created a new sterile compounding entity called "outsourcing facilities," and established track and trace requirements for prescription drugs.
- The Cures Act of 2016 streamlined and added flexibility to the drug development and approval process as well as allowing for more patient experience data during the process.
- The FDORA of 2022 encourages clinical trial diversity, provides reforms to the FDA accelerated approval process, updates the regulatory process for cosmetics and enhances the FDA's oversight of infant formulas.
- The primary goal of the FDCA is to protect the public; however, there is also a trend away from direct regulation to indirect regulation.

Study Scenarios and Questions

A patient asked the pharmacist, "When did the United States first start regulating drugs under the FDCA?" The patient continued, "Why do there have to be so many other laws besides the FDCA, such as the DPC/PTRA, the PDMA, the FDAMA, the FDAAA, the DQSA, the 21st Century Cures Act, just to name a few? Why can't they just amend the FDCA?" Discuss how the pharmacist should answer the patient?

The Food and Drug Administration

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 U.S. 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 http://www.fda.gov.

The agency is structured around the concept of the national headquarters, which provides policy and decision making, together with an extensive field force of professionals throughout the country, which provides additional decision making and regulatory enforcement. The FDA consists of nine Center level organizations and

13 Headquarter (HQ) Offices. For example, the Center for Drug Evaluation and Research (CDER) makes sure safe and effective drugs are available to improve the health of people in the United States while the Center for Biologics Evaluation and Research (CBER) regulates biological products for human use.

A partial listing of the Centers and Offices are:

- The Center for Drug Evaluation and Research (CDER)
- The Center for Biologics Evaluation and Research (CBER)
- The Center for Devices and Radiological Health (CDRH)
- The Center for Food Safety and Applied Nutrition
- The Center for Tobacco Products
- The Center for Veterinary Medicine
- The National Center for Toxicological Research
- The Oncology Center of Excellence
- The Office of Regulatory Affairs
- The Office of Operations

The FDA Overview Organization Chart can be accessed at: https://www.fda.gov/about-fda/fda-organization/fda-organization-charts.

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, 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 will 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. Before issuing a final guidance, the Agency will publish draft guidance and solicit the input of stakeholders. The FDA has issued several guidance documents (some of which will be referred to in this book). Guidance documents are neither legally binding nor legally enforceable. Nonetheless, these guides represent the agency's current thinking on a particular subject and should be followed. To not follow the recommendations in a guidance, especially if specific regulatory or statutory requirements are cited, could lead to FDA investigation and possible enforcement action.

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 selection of members from the list of nominees. Committee size ranges from nine to 15 members. Although the FDA is not obligated to follow a committee recommendation, it often does.

Take-Away Points

- The FDA is a component of DHHS, and although the commissioner is accountable to the secretary of DHHS, the president appoints the commissioner with the confirmation of the Senate.
- The agency is divided into Centers and Offices under the Office of the Commissioner
- Two examples of Centers include the Center for Drug Evaluation and Research (CDER) (which performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States) and the Center for Biologics Evaluation and Research (CBER) (which regulates biological products for human use under applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act).
- The FDA regularly relies on advice from outside experts appointed to standing advisory committees.
- The FDA interprets the FDCA through both rulemaking (regulations) and by means of guidance documents.

Study Scenarios and Questions

The FDA issued a final compliance guidance related to pharmacy compounding. In the guidance, the FDA clarified which activities compounding pharmacies could lawfully engage and which activities the FDA considered unlawful. The owner of the compounding pharmacy directed the staff pharmacists to engage in activities that the FDA considered unlawful. When challenged by a staff pharmacist, the owner replied that those are merely FDA opinions and not legally enforceable. How should the staff pharmacist respond to the owner?

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

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)).
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> (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 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 articles specified in clause (A), (B), or (C).
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> (2) The term "counterfeit drug" means a drug which, or the container or labeling of which, without authorization, 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 represented 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 supplement to them,
> >
> > (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, 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, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting 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 definition of drug (see preceding subsection (g)), 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 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 manufacturer, 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 manufacturer 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 manufacturer'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 manufacturer 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 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 ingredients normally considered drugs might not be classified as 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, provide stimulation and tranquilization, and promote 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 five to four 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)). The Supreme Court decision played a role in stimulating Congress to enact legislation in June of 2009, known as the Family Smoking Prevention and Tobacco Act (P.L. No. 111-31), granting the FDA authority to regulate tobacco products. The FDA may now regulate the contents of tobacco products, require disclosure of product contents, prohibit certain additives, require more effective warnings, and strictly control or prohibit marketing and sales campaigns, especially those directed at children.

The latest tobacco controversy involves electronic cigarettes and other "vaping" devices. Despite widespread societal concern, research has not yet determined the safety of these products. In 2009, the FDA declared that e-cigarettes were unapproved drug/device combination products, which resulted in their removal from the market. Manufacturers of these products, however, successfully challenged the FDA's assertion. The U.S. Court of Appeals for the D.C. Circuit found for the manufacturers on the basis that the agency can regulate the products under the 2009 Tobacco Act, and that they are not drugs or devices unless marketed for therapeutic purposes (*Sottera, Inc. v. Food & Drug Administration*, 627 F.3d 891 (D.C. Cir. 2010)). Subsequently, applying its authority under the Tobacco Act, the FDA finalized a regulation effective August 8, 2016, which extends its authority to all tobacco products, including e-cigarettes, cigars, hookah, pipe tobacco, and nicotine gels (https://www.federalregister.gov/documents/2016/05/10/2016-10685/deeming-tobacco-products-to-be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the). The regulation requires that retailers not sell the covered tobacco products to those under 18 and must verify age with photographic identification, unless the person is over the age of 26. Companies must warn consumers that nicotine is addictive and must submit new and existing products for FDA approval; however, they could continue selling the products pending the FDA's review. The FDA received applications to review millions of applications by the September 2020 deadline, and by 2023, the FDA had authorized 23 tobacco-flavored e-cigarette products and devices. In 2022, Congress also clarified that the FDA

had the authority to regulate tobacco products containing nicotine from any source, including non-tobacco (or synthetic) nicotine. The FDA received nearly 1 million applications in 2022 to review products for non-tobacco products.

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 through any media 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 vs 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 from part C when consumed in their ordinary manner, because when ingested, all foods affect the structure or function of the body in some manner merely due to 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 because their labeling contains health claims.

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 or enteral 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, B_6, B_{12} combination products for hyperhomocysteinemia. Medical foods must be specially formulated, not naturally occurring, and must provide nutritional requirements that would be impossible for the patient to meet through a normal diet. The FDA guidance, revised in 2016, provides examples of diseases and conditions for which a medical food may be marketed and examples of labeling statements that would be considered misbranding (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-frequently-asked-questions-about-medical-foods-second-edition).

Nutraceuticals and Functional Foods

Some believe that the FDA should recognize additional classifications of food products such as "nutraceuticals" and "functional foods." The vague and

broad category of nutraceuticals would include any substance that may be considered food or part of food and that provides health or medical benefits, including the prevention and treatment of disease. Such products would include nutrients; genetically engineered foods; some cereals, soups, and beverages; and many fruits and vegetables because they contain such health-related isolates as vitamins, minerals, and omega-3 fatty acids. 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 related category of product some would like distinguished by law is one called "functional foods." These include foods or nutraceuticals 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. Probiotics are yet another example of products that would likely fall into this category. Probiotics are defined as live microorganisms that, when administered in adequate amounts, produce healthy results. However, many products that might be considered nutraceuticals or functional foods are regulated as dietary supplements and would likely be exempted from parts of the drug definition (discussed later).

Health Claims for Foods

There is a contentious history between the FDA and food manufacturers who have made health claims for their products. One controversy arose in the 1980s 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 has 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 countered that the product was a special dietary food, not a drug. Deciding for the company, the court found that the FDA permitted some foods to be labeled with appropriate health-related messages. The court noted that the FDA was still trying to determine what types of health-related messages would be appropriate and, while doing so, had allowed manufacturers of other products (e.g., Kellogg's All-Bran, fish oils) to continue making health claims. 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 NLEA of 1990 (P.L. 101-535) that amends § 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. FDAMA 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. Alternately, the FDA will approve a health claim if based on an authoritative statement from certain scientific bodies. Pursuant to the NLEA, 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).

Even when FDA regulation authorizes a health claim, food manufacturers may still wander over the food/drug line if they exceed the strict limits and restrictions of that regulation. For example, the FDA issued a regulation (21 C.F.R. 101.81) authorizing a health claim associating soluble fiber from whole grain oats with a reduced risk of coronary heart disease. Pursuant to the regulation, the manufacturer may also include a statement that the reduced risk of coronary heart disease occurs by lowering blood total and LDL cholesterol. General Mills labeled its Cheerios Toasted Whole Grain Oat Cereal with the claims: "You can Lower Your Cholesterol 4% in 6 weeks,"

and "Did you know that in just 6 weeks Cheerios can reduce bad cholesterol by an average of 4%?"

The FDA issued a controversial warning letter to General Mills in May of 2009, contending that these claims indicate that Cheerios is intended for use in lowering cholesterol, and, therefore, preventing and treating the disease of hypercholesterolemia, thus making Cheerios an unapproved new drug. The FDA took the position that these claims are separate, stand-alone claims are different from the permissible health claim that General Mills also included on the box; and, even if the claims were part of the permissible claim, they would not qualify because the regulation does not allow attributing any degree of risk reduction for coronary heart disease. General Mills removed the claim and replaced it with a vaguer statement that the FDA approved (https://wayback.archive-it.org/7993/20171101111921/https://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/CFSAN/CFSANFOIAElectronicReadingRoom/ucm303434.htm).

Dietary Supplements vs 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 and the FDA commonly regulated the products as drugs. After intense lobbying, Congress reacted by passing the DSHEA of 1994 (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. For this reason, the FDA cannot require premarket approval of dietary supplements as it does 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 upon which it relies to substantiate the product's safety and efficacy. DSHEA also generally prohibits the FDA from regulating dietary supplements as food additives. Because food additives require premarket approval by the FDA, Congress wanted to ensure that the FDA did not attempt a backdoor approach at requiring premarket approval. Being stripped of premarket approval authority means that the agency must 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; or
4. Statements describing the general well-being from consumption of a nutrient or dietary ingredient (e.g., "energizer," "relaxant," "muscle enhancer").

DSHEA thus exempts dietary supplements from part C of the drug definition by permitting structure/function claims. For example, a seller can 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; for more information also see the FDA website at: https://www.fda.gov/food/food-labeling-nutrition/label-claims-food-dietary-supplements).

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 following 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

As discussed, DSHEA greatly restricts the FDA's premarket authority over dietary supplements and exempts dietary supplements from part C of the drug definition. DSHEA does not generally exempt supplements from part B of the drug definition, and the issue of whether suppliers can make health or disease claims without risking their product becoming a drug is complicated. 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 FDA must approve the health claim by regulation pursuant to the "significant scientific agreement" standard. By 1999, the FDA had approved approximately 11 health claims by regulation 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 of Appeals agreed with the plaintiffs and felt that complete suppression of health claims, unless they are false or misleading, is too restrictive, when disclaimers (e.g., "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 regarding 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 evaluates health claims. The agency now essentially allows two types of health claims, unqualified and qualified, for both foods and dietary supplements. Unqualified health claims (those requiring no disclaimer) are allowed if authorized by the agency by means of a regulation, because the dietary supplement met the significant scientific agreement test. Qualified health claims (those that must contain a disclaimer as 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 only when there is more evidence for the claim than against it. The qualified claim must be truthful and not misleading and it must 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. For more in-depth information on health claims for foods and dietary supplements, refer to the FDA website at https://www.fda.gov/food/food-labeling-nutrition/label-claims-food-dietary-supplements.

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 its 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, which naturally contains small amounts of monacolin K, 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, which is derived from and identical to monacolin K. 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 Pharmanex was manufacturing and marketing lovastatin and not the traditional red yeast rice. Pharmanex retorted that, nonetheless, lovastatin was present in some foods marketed in the United States 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 at such levels 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 more as foods than as drugs, the FDA can remove a dietary supplement from the market on the basis of public safety only if the FDA 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 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 increased the risk of serious adverse events, including heart attacks, strokes, and death.

The passage of the regulation was hastened after highly publicized accounts of EDS use that led to the death of 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)). In a lawsuit against the FDA by another EDS manufacturer (*NVE, Inc. v. Department of Health and Human Services*, 463 F.3d 182 (3rd Cir. 2006)), the court also sided with the FDA, ruling that plaintiffs could not present additional evidence about EDS but rather are limited to review of the FDA's administrative record.

The Dietary Supplement and Nonprescription Drug Consumer Protection Act

The EDS situation prompted Congress to enact serious adverse event reporting requirements for dietary supplement manufacturers in December of 2006 in a law titled, the Dietary Supplement and Nonprescription Drug Consumer Protection Act (P.L. 109–462). This law adds two parallel, mandatory, serious adverse events reporting systems: one for nonprescription drugs and the other for dietary supplements. Manufacturers, packers, or distributors whose name appears

on the label must submit to the Secretary of Health and Human Services (through the MedWatch program, described later) any report of a serious adverse event within 15 business days. They also must submit any subsequent medical information received within 1 year of the initial reported event. Product labeling must include either the supplier's domestic address or a continuously operating toll-free telephone number so consumers can report serious adverse events. Suppliers must also maintain records related to each report for 6 years and allow inspection of these records. The FDA published a guidance in October of 2007 and revised it in 2013 to assist the dietary supplement industry in complying with the law (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-questions-and-answers-regarding-adverse-event-reporting-and-recordkeeping-dietary).

Criticisms of DSHEA

DSHEA has proven controversial, and critics of the law have identified three major concerns. First, they contend that the law allows the marketing of unsafe dietary supplements and 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 supplements 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.

In response to this third concern over quality standards, the FDA issued a final rule in June of 2007 (72 Fed. Reg. 34752 (June 25, 2007)) requiring that dietary supplement manufacturers comply with the 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. Dietary supplements containing contaminants or lacking the ingredient they represent would be considered adulterated or misbranded. However, because dietary supplements do not require FDA approval, the FDA will generally not identify products in violation of the CGMP before they reach consumers. An investigation by the New York Attorney General's office released in 2015 found that four of five of the store brand dietary supplements it tested from GNC, Target, Walgreens, and Walmart did not contain the active ingredients listed on the labels (http://well.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers/). The office issued cease and desist letters to the companies, demanding they stop selling their store brand supplements.

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, it is completely legal for pharmacists to counsel, educate, and provide advice to patients about the use of a supplement product for a disease, and they should do so when appropriate. 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 in order 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 vs Devices

Before the passage of the MDA of 1976 (discussed later in the chapter), 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 in order to regulate them, 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," as defined under the FDCA, 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. These products are called combination products and the FDA has provided guidance to companies as to how these combination products will be regulated. The FDA has stated that many factors may determine whether a combination product will be regulated as a device or a drug. The FDA often looks at the primary mechanism of action of the combination product but will also consider the following:

- 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 FDA's guidance document related to classifying products as drugs or devices provides a much more in-depth explanation at https://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm. For more information on the FDA's Request for Designation, please refer to https://www.fda.gov/combination-products/rfd-process.

Drugs vs Cosmetics

A cosmetic may become a drug if its intended use fits under the drug definition. *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 credulous" consumer would believe. On the basis of this standard and the manufacturer's claims, the court found that the lotion was a drug because of the structure/function claims 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.

Some products are both cosmetics and drugs. For example, shampoo is a cosmetic because its intended use is to clean the hair. However, antidandruff shampoo is both a cosmetic and a drug since its intended purpose is to treat dandruff. Other examples of products that are both cosmetics and drugs, include deodorants that are also antiperspirants and toothpastes that contain fluoride (https://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm2005209.htm).

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 information 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 misbranding 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 always 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 for a drug. 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 program" 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 as important today because each is subject to regulation by the FDA and must contain all of the information approved by the FDA (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 *United States Pharmacopeia* (*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" (http://www.homeopathicdoctor.com). The controversial premise of homeopathy is that the more dilute the substance, the more potent it is. 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 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.

Since the drug definition includes articles that are recognized in the *HPUS* or its supplements, homeopathic drugs are subject to the same regulatory requirements as other drugs, including premarket approval. However, the FDA has not applied the drug approval laws to homeopathic drugs and has chosen not to require proof of the safety and efficacy of these products. As a result, no drug products currently marketed and labeled as homeopathic have received FDA approval. In

light of a dramatic increase in the marketing and sales of homeopathic drugs and the questionable promotional and labeling practices of some manufacturers, the FDA now believes enforcement is necessary because of public health concerns. Rather than require all homeopathic drug products to obtain approval, which would not be practical, in December of 2022, the FDA finalized guidance on its intent to apply a risk-based priority enforcement approach to homeopathic drug products based on the following categories of products (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-products-labeled-homeopathic-guidance-fda-staff-and-industry):

- Products with reports of injury that, after evaluation, raise potential safety concerns
- Products containing or purporting to contain ingredients associated with potentially significant safety concerns
- Products for routes of administration other than oral and topical
- Products intended for the prevention or treatment of serious and/or life-threatening diseases and conditions
- Products for vulnerable populations
- Products with significant quality issues

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.

Take-Away Points

- The term "drug" has a very broad meaning as defined under the FDCA, and includes any articles intended for use in disease or intended to affect the structure or function of the body.
- Foods are excluded from Part C of the drug definition, raising the issue of what is the definition of food for the purposes of Part C.
- Foods that fall into either the category of "special dietary foods" or "medical foods" are excluded as drugs even though they are marketed with the intent of meeting certain health needs and may be prescription only.
- A food could become a drug if it makes a disease or health claim, unless the claim has been approved by FDA regulation or by "significant scientific agreement."
- DSHEA defined and created dietary supplements as a special class of products.
- A product that meets the legal definition of a dietary supplement may make four types of nutritional support statements without running afoul of Part C of the drug definition.
- A product that meets the legal definition of a dietary supplement may make an "unqualified" health or disease claim without being categorized as a drug if the FDA has approved the claim by regulation, because the claim meets the significant scientific agreement standard.
- A product that meets the legal definition of a dietary supplement may make a "qualified" health or disease claim even though the claim does not meet the significant scientific agreement test provided the claim is not misleading.
- Dietary supplement products containing drugs are likely drugs unless the dietary supplement was approved prior to the drug.
- As the ephedra product situation demonstrates, the FDA can remove a dietary supplement from the market only if it can prove the product is adulterated, meaning under DHSEA that the product presents a significant or unreasonable risk of illness or injury.
- The Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006 requires manufacturers of dietary supplements and nonprescription drugs to warn of serious adverse events.
- Current criticisms of DSHEA include that the law prevents the FDA from evaluating unsafe products prior to market entry and makes it very difficult for the agency to remove unsafe products from the market.
- Since 2007, the FDA has required that the dietary supplements must comply with the CGMP to prevent misbranding and adulteration and must evaluate the identity, purity, quality, strength, and composition of its products. However, the FDA has no authority to inspect the products prior to marketing.
- Pharmacists play an important role in counseling patients in the use of dietary supplements and should direct them to products labeled as conforming to USP or NF standards, if possible.
- The distinction between device and drug can blur and a device could become a drug based on its intended use; however, the MDA generally gives the FDA adequate authority to regulate devices without taking that step.
- A cosmetic could become a drug based on its intended use, and courts will likely apply the ignorant, unthinking consumer standard to make a determination.

- Some products are both cosmetics and drugs.
- The definitions of label and labeling are different. Any written, printed, or graphic matter "accompanying" an article is labeling, making the definition of accompanying important for distinguishing labeling from advertising.
- The *USP* and the *HPUS* are official compendia under the FDCA. The USP establishes drug standards and the HPUS establishes homeopathic product standards.
- The FDA intends to implement risk-based priority enforcement of homeopathic drug products.

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 or both.
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.

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 the natives of one of the tribes added a certain wild root, known as acumana, to many of the dishes they cooked for added flavor and nutritional value. They also chewed the root 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 food, drug, or dietary supplement.

3. Based on the facts in this case, is Acuxen most likely a food, drug, or dietary supplement, or all three and why? (To answer this question, you must consider both the composition of Acuxen and the indication. How does the *Nutrilab* case play into your analysis?)
4. If Sue made the root product as a topical patch, why might your answer be different?
5. Assuming 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? Why or why not?
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

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.
>
> (k) The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other 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.
>
> (v) 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 at the end 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.

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 § 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 § 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 sale or dispensing a counterfeit drug. Counterfeit drugs are a significant problem in the United States, and this section clearly places responsibility on the pharmacy and pharmacist to help to ensure the integrity of the drug distribution system and the drugs they purchase and sell.

Pharmacists who repackage or relabel drugs, either prescription or OTC drugs, must pay particular attention to § 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 § 302, the FDA can bring an injunctive action against the violator to cause it to cease its illegal activity. Under § 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 § 302 and the realization that minor violations of the act should not be subject to criminal prosecution or seizure actions, Congress added § 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 repackaging 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.

These two decisions, collectively are known as the "Park Doctrine," established that corporate officials can be personally prosecuted without proof that they acted intentionally or with negligence, even if they had no knowledge of the offense. After years of dormancy, the FDA announced that it will increase enforcement of the Park Doctrine against corporate officers, and in 2011 published criteria that it will consider in such prosecutions (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual). The FDA has been frustrated that large fines against manufacturers for marketing violations, such as fines of $1.4 billion against Eli Lilly in 2009, $2.3 billion against Pfizer in 2009, $3 billion against GlaxoSmithKline in 2012, and $2.2 billion against Johnson and Johnson in 2013 seem not to have deterred violations of the FDCA.

The FDA hopes that imposing personal liability will change the corporate culture. To that end, the FDA successfully obtained criminal convictions in 2016 against both the president and the COO of an egg-producing company for selling eggs contaminated with salmonella (*United States v. DeCoster*, 828 F.3d 626 (8th Cir. 2016), cert. denied May 22, 2017). The court agreed that the officers were criminally liable, even though the officers had no knowledge of the contamination.

Product Recalls

One method of removing adulterated or misbranded products in interstate commerce is by means of recall, either voluntarily by the manufacturer, by FDA request, or by FDA mandate. Prior to the passage of the FDAAA in 2007, the FDA did not have the statutory authority to order a product recall. Now, the FDA has limited authority to do so for certain products such as medical devices, biological products, and foods, but not for drugs (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual). If a drug manufacturer does not respond appropriately to an FDA recall request, the FDA has the authority to take seizure or injunction action. For any type of recall, the FDA has 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. The FDA posts information about drug product recalls on its Enforcement Reports website: https://www.fda.gov/Safety/Recalls/default.htm. In January of 2018, the FDA announced that recall classifications can take weeks, even months, and since the public benefits by having recall information as soon as possible, the agency decided that henceforth it will commence posting "not-yet-classified" recalls (https://blogs.fda.gov/fdavoice/index.php/2018/01/fda-to-expedite-release-of-recall-information/). Many pharmacy publications and state pharmacy boards also provide notices of recalled products.

A pharmacist is responsible for knowing which drug products have been recalled. Providing 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.

Take-Away Points

- Most violations of the FDCA are either misbranding or adulteration, or both.
- Violators, including pharmacists, of the FDCA are subject to strict liability; however, if the violation occurred in good faith, penalties will not likely be imposed if the violator complies with the FDA investigation.
- The FDA has authority to enforce the FDCA in several manners, ranging from criminal actions to warning letters.
- Corporate officers of pharmaceutical companies can be prosecuted for corporate violations of the FDCA pursuant to the Park Doctrine, even if they had no knowledge of the violations.
- The FDA has the authority to order recalls for certain products, but not drugs, and pharmacists are responsible for knowing when a product has been recalled.
- Product recalls are divided into three classes, depending on the probability and severity of adverse health consequences.

Study Scenarios and Questions

1. A pharmacist received a bottle of cephalosporin capsules. Unknown to the pharmacist, the capsules 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. Assuming that the product is misbranded and 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. Previously the drug had always been in a clear solution. The pharmacist dispensed the drug for IV administration. The drug was contaminated and injured the patient. Assuming that the product is adulterated, explain whether the pharmacist has violated the FDCA, and if so, whether the pharmacist might face sanction by the FDA.
3. A pharmaceutical company issued a Class I recall of one of its drug products. Two months later, two bottles of the drug product were discovered in the inventory of a community pharmacy. The pharmacy argued to the FDA that (1) it had no knowledge of the recall; (2) even if it had knowledge, it had no responsibility to remove the products from its inventory; and (3) possessing the products for resale is not a violation of the FDCA. Are the pharmacy's arguments valid?

Adulteration

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 unsanitary 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

A drug may be adulterated under the FDCA, 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

Note that the key word in these provisions is "may." 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 relatively few manufacturing plants than the thousands of drug products that these plants produce. Second, the health and safety risk to the public are much lower if the FDA can prevent adulteration rather than wait and remove an adulterated product from the market.

Although the adulteration provisions would seem to apply to manufacturers more than pharmacies, pharmacies can violate the adulteration provisions. Some examples include: a pharmacy that counts tablets on a dirty counting tray or on a tray where the residue of the previous drug counted remains on the tray; a pharmacy that repackages drug products for storage in containers that may contaminate the product; or a pharmacy that stores inventory in a room where the temperature is not adequately controlled.

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. For example, assume that a pharmacist received a prescription to compound a drug contained in the *USP* pursuant to *USP* standards. The pharmacist compounded the drug using a different procedure and with different inactive ingredients than specified in the *USP*, but labeled the product with the same drug name as specified in the *USP*. The drug would be both misbranded and adulterated. If, however, the pharmacist (after obtaining the prescriber's approval to make the changes) reflected those changes from the *USP* standards on the label, the compound would not be either misbranded or adulterated, even if labeled with the drug name as contained in the *USP*.

Current Good Manufacturing Practice

Section 501(a)(2)(B) specifically declares that a drug is adulterated unless it is manufactured in accordance with "current good manufacturing practice" (CGMP). 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 or the pharmacy is also registered as an outsourcing facility.

Manufacturers must be registered with the FDA and are normally inspected by the FDA for compliance with the 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. The FDA selects drug products 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 subpotency, 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 or issue an injunction to stop the manufacturer from making the product.

Product Tampering

In response to the intentional contamination of OTC 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-evident packaging. Violation of this regulation may be deemed adulteration, misbranding, or both.

A tamper-evident 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-evident packaging, not tamper-proof packaging, because technology does not exist to eliminate the risk of tampering completely.

Take-Away Points

- A drug is adulterated, even if pure, if subject to conditions that "may" contaminate it or if its manufacture is not in conformance with the CGMP.
- A drug is adulterated if its strength, quality, or purity differs from compendia standards, unless stated on the label or if its strength, quality, or purity differs from what is stated on the label.
- The CGMP is a set of regulations establishing minimum standards for manufacturing methods, facilities, and controls.
- OTC drugs not packaged in tamper-evident packaging, as required by regulation, may be considered both adulterated and misbranded.

Study Scenarios and Questions

1. A pharmacist counted cephalosporin capsules on a counting tray that contained powder from penicillin tablets that had been counted previously and dispensed the capsules to a patient who is allergic to penicillin. The patient suffered anaphylaxis. Explain how this might constitute adulteration pursuant to the adulteration statute.
2. A pharmacy received a prescription for a drug product compound containing 2% active ingredient. The pharmacy compounded and dispensed the compound and labeled it as containing 2% active ingredient. In reality, the product only contained 1% of active ingredient. Explain how this might constitute adulteration pursuant to the adulteration statute.

Misbranding

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

> (a) If its labeling is false or misleading in any particular. Healthcare 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-evident 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 often has used the misbranding provisions of the act to prevent manufacturers from marketing products in violation of the law. Most of the misbranding provisions are also applicable to pharmacies.

False or Misleading Labeling

That a drug's labeling shall not be false or misleading under § 502(a) is fairly self-explanatory. The FDAMA added the provision regarding healthcare economic information (HCEI). Before the FDAMA, the subject of drug manufacturers supplying pharmacoeconomic information to healthcare 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, HCEI provided to formulary decision makers is permissible as long as the information is accurate and reliable.

Habit-Forming Drugs

Before the FDAMA, § 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 contains 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 the 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 § 502(f). The FDA classifies these drugs as prescription drugs, which makes them exempt from the requirements of § 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 elsewhere in the text).

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

Section 502(i)(3) states that a drug is misbranded if it is sold under the name of another drug. Note the similarity between the definition of counterfeit drug (§ 201(g)(2)) and sections 502(i)(2) and (3). A pharmacist who dispenses a generic drug and labels it with the trade name drug might be found to have violated § 301(i)(3) as well as § 502(i)(3). A pharmacist who dispenses a placebo labeled as a certain drug might likewise have violated those two sections as well as § 502(i)(2).

Batch Certification

Before the FDAMA, § 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 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 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 (A, C); https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-otc-human-drug-products-questions-and-answers; 21 C.F.R. § 201.66):

- The name and address of the manufacturer, packer, or distributor
- Location of expiration date
- Control numbers such as lot or batch code
- Principal display panel
- 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 net quantity of the contents of the package
- Declaration of the presence of FD&C Yellow No.5 and/or FD&C Yellow No. 6
- Tamper-evident labeling
- Cautions and warnings needed to protect the consumer such as what to do if an overdose occurs
- Adequate directions for use (as discussed previously)
- A "Drug Facts" panel (**Figure 2-1**) 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)
  - Uses (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)

Drug Facts

Active ingredient (in each tablet) ***Purpose***

Chlorpheniramine maleate 2 mg . . . . . Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:

■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings

Ask a doctor before use if you have

■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis

■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product

■ you may get drowsy ■ avoid alcoholic drinks

■ alcohol, sedatives, and tranquilizers may increase drowsiness

■ be careful when driving a motor vehicle or operating machinery

■ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.

Keepout of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours;
children under 6 years	ask a doctor

Other information store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatized starch

Figure 2-1 Drug facts label.

Reproduced from the U.S. Food and Drug Administration, OTC Drug Facts Label, http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143551.htm

    - Stop use and ask a doctor if (listing of signs of toxicity and other reactions requiring immediate discontinuation)
    - "If pregnant or breastfeeding" warning
    - "Keep out of reach of children" and accidental overdose/ingestion warning
- Directions
- Other information (as required by the monograph, by regulation, or in the approved labeling)
- Inactive ingredients (listed in alphabetical order)
- Questions? or Questions and Comments (followed by a telephone number)

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.

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 by 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. (A drug can also be both OTC and prescription, depending on how it is switched from prescription to OTC status.)

Prescription Drug Labels and Labeling

As noted earlier, prescription drugs are labeled for the healthcare professional, not 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 (e.g., "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 refers to when a single dosage unit of a drug is packaged for direct administration to a patient. 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 information as a commercial container because of the package size. Thus, the FDA's compliance policy guidance specifies the manufacturer's label on the unit dose container of a solid or liquid oral dosage form prescription drug to include (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-430100-unit-dose-labeling-solid-and-liquid-oral-dosage-forms):

- 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 and 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 number of dosage units contained, if more than one dosage, and the strength per dosage unit
- The statement "Warning: May be habit forming" where applicable
- The controlled drug symbol if required by the DEA

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 healthcare 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).

Healthcare professionals had not found the package insert very useful and many did not use it as their primary source of drug information. They found that the format and content of the insert made 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 healthcare 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 and made the regulation final in January 2006 (71 Fed. Reg. 3922-01; 21 C.F.R. parts 201, 314, and 601).

The updated 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 healthcare 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 healthcare 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 healthcare 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 to facilitate discussion between the healthcare professional and the patient regarding the 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.

The 2006 package insert requirements applied only to drugs whose NDAs were submitted after June 30, 2006, and were phased in gradually for drugs approved 5 years prior to June 30, 2006. The FDA hopes manufacturers of other drug products will comply voluntarily.

Online drug labeling information, including the package insert and labeling history, for most FDA-approved drugs can be accessed at Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). In addition, healthcare professionals and consumers can access the DailyMed website, an

information clearinghouse provided through the National Library of Medicine and accessible at http://dailymed.nlm.nih.gov/dailymed/about.cfm; its objective is to provide the most up-to-date drug labeling information.

Proposed Electronic Distribution of Package Inserts

After having considered this issue for several years, in December of 2014, the FDA issued a proposed rule that, if finalized, would require that manufacturers replace paper distribution of the package insert with electronic distribution (https://www.federalregister.gov/articles/2014/12/18/2014-29522/electronic-distribution-of-prescribing-information-for-human-prescription-drugs-including-biological). There would be no change to the substantive content of the insert. The FDA believes the change to electronic form is necessary because prescribers often do not receive the paper package insert and pharmacists often complain about the paper form having small font size, thin paper, and multiple folds, making it difficult to read. The agency is also concerned that changes in prescribing information do not appear in the printed package insert until several months later.

The proposed rule would require manufacturers to submit updated labeling information to the FDA's website (https://labels.fda.gov) within 2 days of a labeling change. It also requires manufacturers to verify that their labeling information is accurate and current and to notify the FDA if this is not true. Manufacturers would be required to revise the label and outside packaging of a product to include the FDA's labeling website and a toll-free number to obtain prescribing information if the Internet is unavailable. The toll-free number must be staffed 24 hours a day, 7 days a week. The FDA proposes to exempt companies from the rule where compliance would adversely affect the safety, efficacy, purity, or potency of the drug, or if it is not technologically feasible or is not appropriate.

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 first implemented black box warnings in 1979 and considers a decision to require a boxed warning to be a dramatic step. Originally, it required the warning for relatively few drugs. In the last decade, however, an increasing percentage of new drug approvals are required to contain black box warnings. Despite the prominence of the boxed warning in the insert and the seriousness of the warning, many critics argue that they are usually ineffective. Reports indicate that many prescribers are either unaware of the warnings or simply do not heed them. Many drugs (e.g., Propulsid, Duract) may not have needed to be withdrawn from the market if healthcare 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. When appropriate, pharmacists should include black box warnings in their patient counseling.

Pregnancy Warnings

Labeling regulations require that the package insert contain information about the risks of using the drug or biological during pregnancy and lactation (21 C.F.R. § 201.57(c)(9)). In December of 2014, the FDA issued a final regulation replacing the prior labeling system that required most drug and biological products be placed into one of five letter categories (79 Fed. Reg. 72063; https://federalregister.gov/a/2014-28241). The more recent labeling regulations became effective on June 30, 2015, and apply to products approved on or after that date. The labeling standards will be gradually phased in for products approved prior to that date. Thus, healthcare professionals should be familiar with both labeling standards for the near future.

Under the prior risk warning requirements, a drug or biological, unless not absorbed systemically and presenting no known harm to the fetus, was placed into one of five letter categories briefly summarized as:

- 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 also must 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 (e.g., 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.

The 2014 regulation replaces this classification system (regarded by the FDA as overly simplistic and subject to misinterpretation as a grading system), with three detailed subsections that the labeling must include to describe the risks. The three subsections are "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential." The "Pregnancy" subsection must provide information relevant to the use of the drug in pregnant women, including dosing and potential risks to the fetus. It must also include information about whether a registry exists that collects and maintains data on the product's use in pregnancy. The "Lactation" subsection will provide information about using the drug during breastfeeding, including the amount of drug in breast milk and potential effects on the child. The "Females and Males of Reproductive Potential" subsection must include information about pregnancy testing, contraception, and infertility as related to the drug. Both the "Pregnancy" and "Lactation" subsections will include subheadings of "risk summary," "clinical considerations," and "data."

National Drug Code Number

Currently, drug products are identified and reported using a unique 10-digit, 3-segment number called the National Drug Code (NDC) (21 C.F.R. §§ 201.2 and 207.35). The NDC assumes one of the following configurations: 4-4-2, 5-3-2, or 5-4-1. 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. The first segment of the code is assigned by the FDA and identifies the manufacturer or distributor (labeler code). The second segment of the code number identifies a specific strength, dosage form, and formulation for a particular firm (product code). The third segment identifies package size and types (package code). The firm supplies the product and package codes.

Although the NDC is 10 digits, the standard for billing and claims submissions is an 11-digit NDC. This is accomplished by inserting a leading zero into one of the segments. The zero is added to the beginning of the first segment if it is four numbers, added to the beginning of the second segment if it is three numbers, or added to the beginning of the third segment if it only has one number.

On July 22, 2022, FDA announced a proposed rule (87 Fed. Reg. 44038), *Revising the National Drug Code Format and Drug Label Barcode Requirements*, that is intended to minimize the impact of FDA running out of 10-digit national drug codes (NDCs) by adopting a single, uniform 12-digit format for FDA-assigned NDCs. The FDA is proposing to change the NDC to 12 digits in length with three distinct and consistent segments and one uniform format. The proposed configuration would be 6-4-2. Additionally, the proposed rule would also revise the drug barcode label requirements, allowing for the use of either linear or nonlinear barcodes, as long as certain standards were met.

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 FDA maintains an NDC directory at https://labels.fda.gov.

Take-Away Points

- A drug is misbranded if its labeling is false or misleading or if HCEI is not accurate and reliable. Section 502 provides for several other labeling requirements and packaging requirements.
- A drug is misbranded unless its labeling contains a list of any active ingredient and the quantity of each. In most situations the labeling must also contain a list of inactive ingredients in alphabetical order.
- OTC drugs must be labeled with "adequate directions for use" directed to the consumer and prescription drugs must be labeled with "adequate information for use" directed to the healthcare professional. Some drugs can be both OTC and prescription, depending upon the intended indications and whether those indications can be labeled with "adequate directions for use."
- A drug is misbranded if it is an imitation of another drug or offered for sale under the name of another drug.
- OTC drug labeling has several points of information, including a Drug Facts panel.
- Prescription drug labels must contain several points of information, although the label of unit dose packaging is allowed to contain less information.
- The package insert has undergone extensive remodeling for the purpose of reducing adverse drug events and making information more accessible, more memorable, and less complex. Required sections of information include Highlights, Table of Contents, Full Prescribing Information, and Patient Counseling.
- The FDA may require a black box warning in the labeling when the use of the drug may lead to death or serious injury.
- The type of risk warnings for a drug's use during pregnancy were changed for drugs approved after June 30, 2015, from a five categories of risk approach to a three detailed subsection approach. The new warning requirements will be phased in for drugs approved prior to June 30, 2015.
- The NDC number identifies drug products and is not only used by the FDA, but also in billing and claim submissions. The first segment of the NDC code number identifies the manufacturer or distributor (labeler code); the second segment identifies the strength, dosage form, and formulation (product code); and the third segment identifies the package size and type of drug (package code).

Study Scenarios and Questions

1. A pharmacist received a prescription for a brand name drug and substituted a generic drug pursuant to state law. The pharmacist labeled the dispensed generic drug using the brand name drug name. Explain whether the pharmacist has violated the FDCA.
2. 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 the situation in Question 1.
3. A patient hands a pharmacist a prescription for Spondicin 20 mg (fictitious), a prescription-only drug. As the patient is waiting for the prescription to be filled, the patient notices that Spondicin 10 mg is available OTC 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?

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 equivalent of a currently marketed drug, it means that drug manufacturers must apply for and receive FDA approval of an 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 FDA'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, 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 healthcare 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 § 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 IND. Application of an IND follows extensive preclinical investigation by the applicant, where through laboratory experimentation and animal testing, the applicant has determined that the drug has potential merit and would be reasonably safe to test in humans.

Investigational New Drug Application

The law requires a sponsor seeking an Investigational New Drug Application (IND) 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 IND application (Form FDA1571) must also include information about the experience and qualifications of the clinical investigators (Form FDA 1572), 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. Second, the process is intended to ensure that the clinical studies are designed properly in order 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 determine safety and 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 subjects 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 further determine 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 subjects. 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 one in 10 drugs demonstrates enough merit to make it this far in the process, however.

Public Registry of Clinical Trials

The FDAAA amended the FDCA to require that NDA sponsors must publish summary information about any post phase 1 clinical trial on a public registry. This public disclosure requirement allows healthcare providers as well as the general public to track the safety and efficacy data generated in the study. Prior to the FDAAA, sponsors only had to post clinical study information for drugs intended to treat serious or life-threatening diseases.

Informed Consent

In all three IND clinical phases, the FDCA (§ 505(i)) requires the investigators to secure the informed consent of the potential participant or a representative for the administration of an experimental drug (21 C.F.R. part 50). This requires that potential participants know the risks, possible benefits, and alternative courses of treatment so that they can make an informed decision about whether to participate in a clinical drug study. 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 must receive the informed consent in writing and sign the form in phases 1 and 2. The same rule applies for phase 3; however, under very limited circumstances, the 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 (21 C.F.R. § 50.24). 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 FDA published draft guidance "Informed Consent Information Sheet" in 2014 to advise IRBs, clinical investigators, and sponsors at https://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm.

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 100,000–200,000 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 PDUFA of 1992 was 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). After the reauthorization of PDUFA in 2012 under the FDASIA, the FDA's goal was to review and act on 90% of priority review NDAs within 6 months and 90% of standard review NDAs within 10 months. In 2015, the agency announced it had met or exceeded those goals. By requiring substantial user fees from product sponsors, PDUFA accomplishes its purpose of reducing FDA review time in three 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. Third, the fees fund upgraded information technology systems to improve efficiency. To review current PDUFA Performance Goals, the FDA posts the information at the following website https://www.fda.gov/about-fda/user-fee-performance-reports/pdufa-performance-reports.

21st Century Cures Act and New Drug Approval

A 2014 report estimated that it takes an average of over 10 years and $2.6 billion for a potential drug to ultimately receive FDA approval (https://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/). In part to address this issue, Congress passed the 21st Century Cures Act in December 2016 with the objectives of streamlining and adding flexibility to the drug development and approval process and creating a more patient focused approach to the process (H.R. 34). To achieve these objectives, the law encourages the consideration of novel clinical trial designs and the incorporation of "real-world evidence" into the decision-making process. Real-world evidence is defined as data regarding the use, benefits, or risks derived from sources other than randomized clinical trials, such as ongoing safety surveillance, observational studies, and registries. It also requires the FDA to consider how patient experience data, including outcomes and preferences, can be used during the approval process. The 21st Century Cures Act does not alter the statutory standards of evidence required for NDA approval or biological licensing but does allow manufacturers more flexibility in meeting those evidentiary standards.

The 21st Century Cures Act also creates or amends four pathways or programs for drugs that treat serious or life-threatening diseases that affect smaller populations or diseases with significant public health risk, including facilitating the development and approval pathway for genetically targeted drugs that meet unmet medical needs; creating a program for the approval of antimicrobial resistant drugs ("superbugs") for limited populations; expanding the orphan

drug program; and reauthorizing the FDA voucher program for rare pediatric diseases. The 21st Century Cures Act also requires a manufacturer to provide the public more information on the availability of its INDs for treatment purposes outside of clinical trials.

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 often is 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 and a letter indicates its therapeutic potential. For chemical type, the designations are (see https://www.fda.gov/drugs/investigational-new-drug-ind-application/drug-development-and-review-definitions):

1. New molecular entity
2. New active ingredient
3. New dosage form
4. New combination of compounds
5. New formulation or new manufacturer
6. New indication (drug product previously marketed by the same firm)
7. Drug already marketed without an approved NDA
8. OTC switch
9. New indication submitted as distinct NDA, consolidated with original NDA after approval
10. New indication submitted as distinct NDA, not consolidated

These types are not mutually exclusive, because a new formulation (type 5) or a new combination (type 4) also may contain a new molecular entity (type 1) or a new active ingredient (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) or O for orphan drug. 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 safe 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 drugs already on the market and offers at best only minor improvements over existing drug therapies. An O rating means the drug is a product that treats a rare disease affecting fewer than 200,000 persons in the United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the US a drug for such disease or condition will be recovered from sales in the US of such drug.

Supplemental New Drug Applications

After the approval of an NDA, a manufacturer usually may not 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" (CBE) supplement may be allowed. The CBE supplement allows the sponsor to implement the change before the FDA approves it. For labeling changes, however, the regulation requires that the change must reflect "newly acquired information" that strengthens a contraindication, warning, precaution, or adverse reaction, and then only if there is sufficient evidence of a causal association. 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 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 NDA 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. The FDA compiles this information into a database called the FDA Adverse Event Reporting System (FAERS) and monitors the data for any new safety concerns (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm).

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 IV Studies

Manufacturers engage in postmarket clinical studies known as phase IV studies for a variety of reasons, including to determine new uses or abuses for a drug or to obtain additional safety or efficacy data for labeled indications. Historically, the FDA has lacked clear statutory authority to require phase IV testing, even when safety controversies had arisen about a drug. FDAMA gave the FDA that authority for "fast-track" drug approval (as discussed later in this text), but it was not until the FDAAA that Congress granted the agency authority to require phase IV testing for any prescription drug. Now, the FDA can require a phase IV study to assess serious risks when adverse event reporting or active surveillance would not be sufficient.

Risk Evaluation and Mitigation Strategy

The FDAAA granted the FDA yet another important safety tool known as Risk Evaluation and Mitigation Strategy (REMS), whereby the FDA can require a drug product sponsor to establish special procedures directed at patient safety. The intent of REMS is to manage known or potential serious risks of the product. The FDA can require a sponsor to include a REMS in a pending NDA or mandate a REMS postmarket when the FDA believes it necessary to ensure that the benefits of the drug outweigh its risks. A REMS will require the manufacturer to submit periodic postmarket assessments of whether the drug's risks are being adequately managed.

A REMS can require a variety of procedures, including distribution of Medication Guides, a patient package insert, and a communication plan aimed at healthcare professionals. For drugs with particularly high potential for harm, a REMS might require "elements to assure safe use," which might include restricted distribution plans, certification of healthcare providers, special training or experience of healthcare providers, patient registries, and similar requirements. In March 2008, the FDA issued a notice requiring that the manufacturers of 25 high-risk drugs, including abarelix, alosetron, clozapine, fentanyl citrate, and thalidomide, must submit REMS plans (73 Fed. Reg. 16313). Certain drugs such as isotretinoin had REMS in place prior to the FDAAA. (*Note:* Although Accutane [brand of isotretinoin] was removed from the market in 2009 by its manufacturer, some generic versions of isotretinoin continue to be marketed.) Subsequently, the FDA approved a REMS for extended-release and long-acting opioid drugs (https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm) and transmucosal immediate-release fentanyl products, and created a restrictive distribution program for these products (https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems). Similarly, in 2017, the FDA notified manufacturers of immediate- release opioid analgesics intended for use in the outpatient setting that their drugs would be subject to REMS.

The FDA has published tables of all drug products with currently approved individual REMS, currently approved shared system REMS, and released REMS at https://www.accessdata.fda.gov/scripts/cder/rems/. Providers and patients can use the tables to determine the REMS requirements for each listed product. Additionally, in 2021, FDA launched a public dashboard for medications with an approved REMS, which can be used as a tool to access data regarding drugs with REMS, and is available at https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems.

Postmarket Labeling

Surprisingly, prior to the FDAAA, the FDA did not have the authority to require manufacturers to include additional safety information or warnings in its labeling after the drug had been marketed. Generally, manufacturers complied with the FDA's requests to edit the labeling; however, on occasion, the changes

were not effected until months after the FDA's requests and only after extensive negotiations occurred. The FDAAA provided the agency with the authority to compel safety-related labeling changes when the FDA becomes aware of a serious drug risk that it believes should be included in the labeling.

Postmarket Drug Safety Information for Patients and Providers

An important feature of the FDAAA required that the FDA develop and maintain a consolidated and easily searchable website for patients and providers, including patient and professional labeling, recent safety information, information about implemented REMS, drug safety guidance documents and regulations, and drug-specific summary analyses of adverse drug reaction reports. Pharmacists, other healthcare professionals, and patients should find the website a valuable resource for drug information accessible at https://www.fda.gov/drugs/drug-safety-and-availability/postmarket-drug-safety-information-patients-and-providers.

The FDAAA established another important safety provision known as the Sentinel Initiative (https://www.fda.gov/safety/fdas-sentinel-initiative). This is a proactive surveillance system designed to detect early signs of medication risk and safety problems. Under the Sentinel Initiative, the FDA has developed a new electronic system that enables it to query a broad array of information data sources, such as electronic health record systems and insurance claims databases, to identify possible postmarket adverse events. The FDA has partnered with the Centers for Medicare & Medicaid Services (CMS) to analyze Medicare Part D claims data, and also will partner with the Veterans Administration as well as an array of private healthcare organizations to analyze their data.

Acknowledging the importance of communicating risk to healthcare providers, patients, and consumers about all FDA-regulated products, the FDA published a risk communication strategic plan in September of 2009 (https://www.fda.gov/aboutfda/reportsmanualsforms/reports/ucm183673.htm). This plan outlines the efforts that the agency will take to release communications and mentions pharmacists as a targeted group to receive this information.

Emergency Use Authorization

The Secretary of HHS can declare that an Emergency Use Authorization (EAU) is appropriate under Section 564 of the FDCA. The EUA allows the FDA to help strengthen the nation's public health protections against chemical, biological, radiological, and nuclear (CBRN) threats, including infectious diseases, by facilitating the availability and use of medical countermeasures (MCMs), including vaccines, needed during public health emergencies. Under an EUA, the FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions when certain conditions are met, including when there are no adequate, approved, or available alternatives.

Manufacturers decide whether and when to submit an EUA request to the FDA. As an example, in late 2020, Pfizer-BioNTech and Moderna both submitted EUA requests to the FDA for their mRNA COVID-19 vaccines, which the FDA issued EUAs shortly after. The FDA has additional information regarding EUAs and the process available on its website at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

Drug Efficacy Study Implementation

The FDA initiated the Drug Efficacy Study Implementation (DESI) program in 1968 in response to the 1962 Kefauver-Harris Amendment requiring that drugs be effective as well as safe. The FDA applied the efficacy requirement retroactively to all drugs marketed after 1938 (pioneer 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 changed its policy and regarded 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 contended that 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 NDAs for post-1962 generic drugs, the FDA compromised by implementing what it called a "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 PTRA.

Drug Price Competition and Patent Term Restoration Act of 1984

The Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman amendment; P.L. 98-417) came to the aid of generic drugs by statutorily creating the ANDA, which had been the FDA's policy for pre-1962 generic drugs. As discussed earlier, an ANDA allows a sponsor to streamline the approval process because it does not have to conduct clinical studies to establish safety and efficacy. Rather, the generic drug sponsor needs only to submit sufficient information to demonstrate that the generic contains the same active ingredient, route of administration, dosage form, and strength as the pioneer drug; is bioequivalent to the pioneer drug; and has acceptable manufacturing methods and control procedures. The FDCA establishes a presumption that

if the products are bioequivalent, 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) and rate of absorption (area under the curve) 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 two important concessions for innovator drug manufacturers. First, the law allows the FDA to grant innovator drugs patent-term extensions. The innovator drug manufacturers lobbied hard for patent extensions 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. It is during this time of patent protection that innovator manufacturers generally must recover the costs incurred during the IND/NDA phase. Patent extensions are available only if the patent has not expired. The second benefit the law provides is market exclusivity for an innovator manufacturer that develops a new chemical entity or a new use for a previously approved drug. Market exclusivity 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. In situations in which new clinical investigations support new indications, dosages, or strengths for a previously approved drug, the FDA can grant 3 years of exclusivity. However, this exclusivity applies only to the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drug products containing the original active ingredient.

In order to ultimately obtain approval for an ANDA, the generic manufacturer must make a patent certification. The law provides four types of certification a generic applicant can make relevant to the patent of the reference drug:

(I) That the NDA holder did not file information on the patent to the FDA
(II) That the patent already had expired
(III) The date that the patent will expire
(IV) That the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic applicant's drug

If the applicant submits a paragraph I or II certification, the FDA will approve the ANDA provided that all other requirements of the application are met. If a paragraph III certification is filed, the approval will likely be effective on the patent expiration date. If, however, a paragraph IV certification is filed, the process gets considerably more complicated. The applicant must notify the patent owner and NDA holder, citing the factual and legal bases for why the applicant believes the patent is invalid. If the patent owner sues the generic applicant, the FDA is automatically enjoined from approving the ANDA for 30 months, unless a court issues a final ruling that the patent is invalid prior to the end of the 30-month expiration period. To encourage generic manufacturers to challenge patents, because to do so is very costly, the law awards 180 days of marketing exclusivity to the first generic applicant to file an ANDA containing a paragraph IV certification. Of course, the generic applicant, if sued by the patent holder, must obtain a favorable court decision on the patent issue to obtain this exclusivity.

Controversies for Healthcare Practitioners

The Drug Price Competition and Patent Term Restoration Act created two controversies for healthcare practitioners. First, the law allows a generic drug to statistically vary in its rate and extent of absorption by plus or minus 20% from the parent and still be considered as bioequivalent. This led to the position by some that if a patient used generic X in 1 month, which was plus 20%, and used generic Y the next month, which was minus 20%, there could be a 40% 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 that the statistical procedure involved would not allow such a variance. The FDA further commented that in analyzing data on generic drugs approved between October of 1984 and September of 1986, the average difference in

absorption between generic and pioneer products was only plus or minus 3.5%, 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 whether a generic drug product could be prescribed and dispensed for an indication that the innovator drug product has been granted exclusivity. 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 the section "Approved Drugs for Off-Label [Unlabeled] Indications").

Drug Manufacturer Controversial Practices

The Drug Price Competition and Patent Term Restoration Act has created some very controversial practices by drug manufacturers. Some of these practices have existed since the Act's passage, but in the past few years, they have captured the attention of Congress and the public because several blockbuster drug patents either have recently expired or will soon do so. One such practice involves an innovator manufacturer producing a generic version of its brand name product, called an "authorized generic," just as its patent is about to expire or be successfully challenged by a generic competitor. The FDA takes the position that the innovator may do this without an ANDA, because the generic and brand name drug products are the same and thus approved under the NDA. This means that the innovator manufacturer can produce the generic and compete directly with a generic manufacturer who filed a successful paragraph IV certification with its ANDA. The generic manufacturer no longer derives as much value from the 180-day market exclusivity and the innovator manufacturer retains some market share it otherwise would have lost.

Another controversy involves the 30-month stay in ANDA approval when the patent holder sues the generic company for patent infringement. Critics contend that many innovator manufacturers sue to obtain the 30-month exclusivity, even though they have very weak legal arguments on their side and no chance of ultimately prevailing. Some manufacturers have piggybacked lawsuits to allow for additional 30-month exclusivity periods, although recent legislation has limited this practice. To make matters even more difficult for generic manufacturers attempting to invalidate patents, innovator manufacturers commonly file secondary patents after the initial patent, covering such things as manufacturing processes, methods of use, and even new tablet coatings. These secondary patents can add to the legal complexities facing generic companies.

Some innovator manufacturers engage in a related practice, often called product hopping. When a product nears its patent expiration, a manufacturer may make some type of product change, such as extended release or using a different salt, and secure an additional patent. The manufacturer will then extensively market the new product, encouraging patients to switch from the old product to the new product, thereby reducing the market for generic versions of the old drug.

Yet another practice that invoked investigations by the FTC, Justice Department, and Congress involves the innovator company paying the generic manufacturer not to market its generic—a practice sometimes called exclusion payments, reverse payment agreements, or pay for delay agreements. Remember that a generic company filing a successful paragraph IV ANDA enjoys a 180-day exclusivity period. To prevent this from occurring, some innovator manufacturers have entered into patent settlement agreements with generic companies. The settlement agreement usually includes payment to the generic manufacturer for all litigation costs plus a significant sum, usually more than the generic manufacturer would make marketing the drug for the 180-day period. The innovator manufacturer still profits significantly by retaining marketing exclusivity for an additional 180 days. Federal court decisions were conflicted as to whether this practice violated the antitrust laws, leading to a U.S. Supreme Court decision in 2013. In *Federal Trade Commission v. Actavis, Inc.*, 133 S. Ct. 2223 (2013), the Supreme Court held that cash payments in these arrangements are not presumptively illegal, but could be illegal as judged under the "rule of reason," meaning that the legality of each arrangement should be judged by weighing its procompetitive benefits against its anticompetitive effects. Although the FTC had hoped the Court would find these arrangements presumptively illegal, it nonetheless hailed the decision as a victory. Since the decision, the FTC has aggressively investigated and challenged pay for delay agreements between drug companies. In 2016, a federal court of appeals decision held that even agreements that do not involve cash are subject to antitrust scrutiny and the Supreme Court refused to hear the case (*King Drug Co. v. SmithKline Beecham Corp.*, 791

F.3d 388 (3rd Cir. 2015); *cert. denied* 137 S. Ct. 446, Nov. 2016)).

Finally, some generic manufacturers have contended that some brand name manufacturers have refused to provide them with samples of the brand name drug that they need for use in clinical trials testing for bioequivalence. They allege that the brand name companies with products subject to REMS are distorting a REMS provision that restricts distributing drugs that are dangerous or subject to abuse.

Generic Drug Labeling Controversies

The law requires that the labeling of a generic drug be the same as that of the innovator drug (§ 355(j)(2)(A)(v)). This has created some significant controversies. In the case of *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), Bristol-Myers held exclusivity rights for 3 years to an indication approved by a supplemental application for one of its drug products. A generic manufacturer sought approval of an ANDA for a generic equivalent to Bristol-Myers's product. Bristol-Myers argued that because the statute requires that the generic labeling be the same as that of the innovator and cannot be the same because of its exclusivity rights, the ANDA must be rejected. The court, however, agreed with the FDA's analysis that the manufacturer's interpretation is at variance with other provisions in the law and legislative intent; that being the new generic drug be safe and effective for each indication appearing in the labeling. The fact that the labeling 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-Myer'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 an innovator drug product could strategically file supplemental indications over several years, precluding any generic competition.

The controversies over identical generic drug labeling took a different twist in a 2011 U.S. Supreme Court Case, *Pliva, Inc., et al. v. Mensing*, 131 S. Ct. 2567. The plaintiffs in this case, injured by a drug's adverse effect, sued the generic drug manufacturer, arguing that the manufacturer had a duty to change its labeling to reflect the known adverse effect. Remember that in the section discussing supplemental NDAs, a drug manufacturer can make certain changes, such as warnings, prior to FDA approval under what is a CBE supplemental NDA. In a 2009 U.S. Supreme Court case, the Court indeed held that the manufacturer of an innovator drug could have changed its labeling under the CBE supplemental NDA to strengthen its warnings and found for the injured plaintiff (*Wyeth v. Levine*, 129 S. Ct. 1187 (March 4, 2009)). In *Pliva*; however, the Court, following the FDA's interpretation of the labeling law, found that generic drug manufacturers are precluded from independently making any changes in their labeling and thus found against the injured plaintiff.

The *Pliva* and *Mensing* decisions create a situation where if an injured plaintiff takes an innovator drug, the plaintiff would have a cause of action against the manufacturer for injuries caused because the manufacturer failed to change its labeling to reflect recently discovered adverse events. However, if that same plaintiff takes the generic drug instead and suffers the same injury, the plaintiff would not have a cause of action against the manufacturer. Consumer groups want this safety loophole closed, prompting the FDA to propose a regulation that would allow generic manufacturers to change their labeling pursuant to a CBE supplement (78 Fed. Reg. 67985 (Nov. 2013)). However, the proposed rule has sparked even more controversy. Although supportive of the FDA's efforts to get safety information to patients and providers, pharmacy associations are concerned that the regulation as written would cause confusion, undermine the public's trust in generic drugs, increase liability to pharmacists, and potentially create generic drug shortages. The generic industry opposes the regulation, arguing that it would increase costs and liability and cause public confusion. The FDA has delayed issuing a final rule for the foreseeable future.

Section 505(b)(2) NDAs

The Drug Price Competition and Patent Term Restoration Act not only statutorily created the ANDA, but also established another streamlined drug approval pathway known as a 505(b)(2) application, which replaced and expanded the old "paper" NDA policy. Under a 505(b)(2) application, the manufacturer is allowed to rely, at least in part, on published safety and efficacy data and/or the FDA's findings for a previously approved drug, thus reducing the number of clinical trials required from the manufacturer. This reduces cost and expedites the approval process. A 505(b)(2) application might be chosen for several reasons. The manufacturer of a drug approved under a previous NDA might use this pathway to receive approval for new indications, relying on the safety data of the previous NDA. A generic manufacturer might choose this route of application instead of a full NDA, when

the generic product cannot be approved under an ANDA because of significant changes from the reference product such as a different formulation, route of administration, or delivery mechanism. The manufacturer of the reference drug, of course, could pursue the 505(b)(2) route for the same types of changes. Depending on the extent of the changes from the reference product, a manufacturer could be granted 3–5 years of market exclusivity.

Drug Competition Action Plan

In June of 2017, the FDA announced a new effort called the "Drug Competition Action Plan." The goal of this Plan is to institute new policies aimed at bringing more competition to the drug market, most notably improving the efficiency of the generic drug approval process. Under the Plan, the agency announced in October of 2017 policies designed to bring complex generic drugs to market more quickly. Complex generic drugs normally require considerably longer in order to obtain FDA approval, primarily because establishing bioequivalence is much more difficult than for other drugs. Additionally, the Plan also focused on closing loopholes that allow brand name drug companies to "game" FDA rules in ways that delay generic competition that Congress intended. Since 2017, the FDA has issued multiple guidance documents (draft and final). Additional information about the Plan, including the FDA guidance documents, can be accessed at https://cacmap.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competition-action-plan.

Over-the-Counter 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, in 1972, 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 FDA 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 rulemaking rather than on a case-by-case basis. The FDA took this approach for several reasons. First, there were between 100,000 and 500,000 OTC drug products on the market, many of which were not approved by the NDA; 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 of the OTC drugs were prepared from only 200 or so 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 publishes a proposed rule in the *Federal Register*. Then, the agency publishes a monograph, identifying which active ingredients are generally recognized as safe and effective (GRASE) 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. Alternately, 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 GRASE or that are misbranded.
3. Category III includes ingredients for which available data 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 that 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. Although 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 continue informally to do what it had been doing by regulation.

In July 2018, the FDA introduced draft guidance with the intent of innovating the OTC drug review approach for determining the safety and effectiveness of nonprescription drugs (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM613666.pdf). The FDA's ultimate objective is to increase the number of drugs approved as nonprescription drugs rather than as prescription drugs without changing the evidentiary standards. The draft guidance proposes two methods that a product sponsor might be able to demonstrate safety and effectiveness when the drug facts label alone is insufficient. One method would be to require the sponsor to provide additional labeling such as informational leaflets, or displays of text or images on websites or mobile applications. The second method would be to require the sponsor to add conditions that the consumer must fulfill, such as requiring the consumer to respond to questions on a self-selection test prior to purchase; or requiring the consumer to view and affirm that they have viewed text or images in a video as to how to appropriately use the drug product. Thereafter, in July of 2022, the FDA published a proposed rule that would establish requirements for a nonprescription drug product that has an additional condition for nonprescription use (ACNU) (87 Fed. Reg. 38313). This proposed rule is intended to broaden the types of nonprescription drug products available to consumers, allowing the ACNU to enable self-selection and appropriate use of a product by the consumer without the oversight of a healthcare practitioner. An example of an ACNU requirement to accomplish this goal may include the consumer having to complete a questionnaire regarding the product before being able to purchase it.

Take-Away Points

- No "new drug" may be introduced into interstate commerce unless the FDA has approved it.
- The FDCA defines a "new drug" as a drug that is not GRASE when used for the conditions labeled, and which has not been used to a material extent or for a material time.
- An approved drug can become a "new drug" if the manufacturer makes certain changes in the product or its labeling.
- The new drug approval process starts with an IND application and requires a substantial amount of information before the application is granted, including pharmacological, pharmacokinetic, and toxicological evaluations.
- During the IND stage, a drug passes through three phases of clinical investigation and the FDA can terminate an IND at any time, if warranted.
- Patient-informed consent is required during all three IND phases with very limited exceptions.
- The IND period culminates with the filing of the NDA for FDA approval and by statute, the FDA has 180 days to act, but significant delays are common.
- The PDUFA of 1992 and its subsequent 5-year extensions have greatly reduced the FDA review time for NDAs.
- The FDA implements a priority classification rating system for new drugs based on chemical type and therapeutic potential, and this rating generally determines how quickly a drug will proceed through the NDA process.
- The 21st Century Cures Act encourages the consideration of novel clinical trial designs and the incorporation of real-world evidence into NDA decision-making. The FDA is required to consider how patient experience data can best be used. The law also creates or amends four pathways or programs for drugs that treat serious or life-threatening diseases that affect smaller populations or diseases with significant public health risk.
- After NDA approval, any changes a manufacturer may wish to make in the production or labeling of the drug are usually made by means of a supplemental NDA, of which there are three procedural categories: prior approval, Change Being Effective (CBE), and very minor changes.
- After marketing, a manufacturer must maintain a postmarketing surveillance program and submit reports of any serious adverse drug reactions and any other pertinent new safety and efficacy information to the FDA when warranted. The FDA maintains this information in an online database (FAERS).
- The FDA has the authority to require a manufacturer to engage in phase IV testing.
- The FDA has the authority to require a manufacturer to develop a REMS, either during the NDA process or postmarket, in order to manage known or potential serious risks of the drug product. An FDA database of drugs with REMS is available online.

- The FDA can compel safety-related labeling changes postmarket.
- The FDA has developed a searchable website for patients and providers, which includes a drug's labeling, safety guidance documents and regulations, and adverse drug reaction reports as well as a proactive surveillance system known as the Sentinel Initiative.
- The FDA may authorize Emergency Use Authorizations (EUAs) for unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions when certain criteria are met, including that there are no adequate, approved, and available alternatives.
- The DESI study commenced in 1968 in response to the 1962 Kefauver-Harris Amendment in order to retroactively evaluate drug products marketed between 1938 and 1962 for efficacy. Drugs marketed prior to 1938 were exempted.
- Prior to 1962, the FDA generally allowed generic drugs to be marketed as not new drugs. Under DESI, the FDA changed policy and regarded these drugs as new drugs.
- Rather than require unapproved generic drugs marketed between 1938 and 1962, the FDA adopted a policy that allowed generic drug manufacturers to submit an ANDA during the DESI review.
- Under an ANDA, a manufacturer must submit proof of bioequivalence to the parent drug and proof of acceptable manufacturing methods and controls but not clinical proof of safety and efficacy.
- The FDA refused to extend the ANDA process to generic drugs marketed after 1962, but did allow submission of a "paper" NDA.
- The paper NDA, however, was not conducive to increasing the availability of generic drugs that, in turn, led to the passage of the PTRA as a legislative solution.
- The Drug Price Competition and Patent Term Restoration Act, enacted in 1984, codified the FDA's ANDA policy, expediting generic drug approval while awarding patent extensions and market exclusivity in certain situations for NDA holders.
- In order to obtain ANDA approval, a manufacturer must make one of four types of patent certification.
- The Drug Price Competition and Patent Term Restoration Act initially created two controversies for healthcare providers, which have largely been put to rest.
- The Drug Price Competition and Patent Term Restoration Act opened loopholes for NDA holders to delay generic competition, including marketing an "authorized generic"; suing the generic company for patent infringement to obtain a 30-month exclusivity; engaging in product hopping; and employing reverse payment or pay for delay agreements.
- The fact that the Drug Price Competition and Patent Term Restoration Act requires the generic drug product's label to be identical to the innovator drug's label has created controversies, both related to the introduction of generic drugs and to drug product liability cases.
- A 505(b)(2) application allows a manufacturer to use published or other existing information to establish safety and efficacy without extensive clinical trials.
- The FDA does not approve OTC drug products individually, but rather on the basis of therapeutic category by means of enacting regulations. Thus, a new OTC drug can be marketed if it meets the relevant monograph standards.

Study Scenarios and Questions

1. A manufacturer of a dietary supplement made a disease claim for its product in such a manner that the FDA deemed that the claim made the product a new drug. The manufacturer responded that it did not deny that the claim would make the product a drug; however, it contended the product is not a "new drug" and thus could be marketed without approval. The manufacturer claims it can submit enough evidence that its product is GRASE and has been used to treat the disease for more than 100 years. Discuss the merits of the manufacturer's argument and whether it might prevail.
2. 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.
3. 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 completely address the patient's concerns?
4. 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 much 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.

5. A manufacturer learns postmarket that its drug is increasingly being linked to an adverse effect not apparent during the IND process. Explain the process required if the manufacturer decides it wants to include a warning in its labeling.
6. As a pharmacist, you inform a patient that the patient's copay will be $15 less if the pharmacist substitutes the generic drug for the brand prescribed. The patient is concerned about quality and asks you whether the generic drug is as safe and effective as the brand name drug and whether the FDA approves generic drugs as rigorously as brand name drugs. How would you completely explain this to the patient?
7. A patient tells you, the pharmacist, that he has heard that the FDA does not approve OTC drug products and he is concerned whether they are safe and effective. Provide a complete explanation for this patient.

Marketed Unapproved Drugs

Based on the preceding discussions, one might be led to believe that, except for some drugs marketed 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 (CPG) published in June of 2006 and revised in September of 2011, the FDA estimated that there are as many as several thousand prescription and OTC drug products marketed illegally without the required FDA approval. The 2006 CPG signified the beginning of what the agency termed its "Unapproved Drugs Initiative" (UDI) and described the FDA's enforcement intentions toward these unapproved products. The FDA stated that since the initiative started, it removed more than 1,000 unapproved drugs from the market (76 Fed. Reg. 58398, 2011). For example, in 2011, the agency launched major enforcement actions against hundreds of marketed unapproved cough, cold, and allergy drug products (76 Fed. Reg. 11794, March 3, 2011). As another example, in July of 2012, based upon reports of medication errors causing serious adverse events, the FDA announced that it would take enforcement action against companies manufacturing or distributing "unapproved" single-ingredient, immediate-release oxycodone products (77 Fed. Reg. 40069).

As explained in the CPG, there are many reasons why both legal and illegal unapproved drug products exist on the market. These reasons include:

- Drug products that were marketed before 1938 with no subsequent changes in labeling or composition. These may legally remain on the market, although the FDA believes there are few of these.
- Drug products currently being marketed and claiming to be grandfathered as pre-1938 drugs that have changed labeling or composition. These drugs are on the market illegally.
- Generic drug products marketed between 1938 and 1962 that the FDA allowed on the market as not "new drugs" if the pioneer or innovator drug had a safe marketing history. (Even though the FDA changed this policy when the DESI review commenced in 1968, some of these drugs still remain on the market, most likely illegally.)
- During that same time period between 1938 and 1962, 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 they were not new drugs or simply because the agency did not take action against them. Some of these drugs remain on the market illegally.
- Drug products being marketed pending a final determination of their efficacy under DESI reviews. (Technically, these drugs are not considered illegally marketed because the FDA has allowed the products to be marketed pending DESI review.)
- Drug products that have been determined to lack evidence of efficacy after the DESI review but have yet to be removed from market. These drugs are being marketed illegally.
- Drug products similar to those pending DESI review, which have never submitted applications for review. These remain on the market illegally.
- Unapproved products by unscrupulous manufacturers that make unapproved and unsupported health claims.
- Illegally marketed OTC drugs, either because monographs do not allow their ingredients or because they were never subject to the OTC review.

In the CPG, the agency explained that the illegally marketed drugs remained on the market because they had to be identified (no easy process) and because removing each product required a considerable amount of scarce FDA resources and time to comply with legal procedures. As a result, the FDA had to prioritize enforcement, with highest priority going to drugs that presented safety risks, lacked

evidence of effectiveness, and involved health fraud. Despite the FDA's attempts to remove unapproved drugs through the initiative, new, unapproved drugs constantly appeared on the market after the issuance of the 2006 CPG. Relying on the FDA's slow enforcement procedures and scarce resources, unscrupulous manufacturers attempted to capitalize on profits before the FDA could force their products off the market. As a result, the 2011 revised CPG announced that any unapproved drugs introduced onto the market after September 19, 2011, would be subject to immediate enforcement action without prior notice and without regard to the enforcement priorities established in the CPG.

However, while the FDA currently still has a website dedicated to unapproved drugs and provides links to guidance documents and resources on the topic, the 2011 revised CPG is listed as withdrawn effective December of 2020 (see https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs). This is because in November of 2020, the Department of Health and Human Services (HHS) announced that it was ending the FDA UDI and withdrawing the 2011 revised CPG in an effort to deal with the rising costs of prescription drugs (85 Fed. Reg. 75331). According to the HHS under the Trump administration, a study of the UDI had found that the drugs subject to the program increased in price drastically and were often subject to drug shortages. HHS asked for information regarding the drugs involved to determine how to best proceed. Then, in May of 2021, under the Biden administration, HHS announced the reinstatement of the UDI (86 Fed. Reg. 28605). In addition to referring to the 2020 action as legally and factually inaccurate, HHS also provided that the FDA would issue new guidance in the future, but until then, would continue to exercise its existing general approach to prioritizing regulatory and enforcement action, which involves risk-based prioritization considering all the facts of a given circumstance. 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. Approved drug products can be identified at the Drugs@FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm).

Take-Away Points

- There may be several thousands of unapproved drug products currently being marketed both legally and illegally.
- The FDA prioritizes enforcement of marketed unapproved drugs with the highest priority to drugs that present safety risks.
- There are several reasons why a drug may be on the market without FDA approval, including that it was marketed prior to 1938; it is a generic drug marketed between 1938 and 1962 that escaped DESI review, is still pending DESI outcome, or just remained on the market despite adverse DESI review; it is a nongeneric drug marketed between 1938 and 1962 that the FDA felt was not a new drug; it is a drug marketed by an unscrupulous manufacturer who intentionally avoided FDA approval for profit purposes.
- Pharmacists can determine if a drug is approved at Drugs@FDA.

Study Scenarios and Questions

A patient is prescribed a brand name drug. The patient asks the pharmacist if generics are available. The pharmacist's research shows generics are available but unapproved by the FDA. The pharmacist tells 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.

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. For example, 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.

Widespread 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 (21 U.S.C. § 360bbb):

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)

The FDAMA also provides that an individual patient acting through a physician may request an investigational drug for the treatment of a serious disease or condition 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 also must submit to the FDA a protocol describing the use of the drug.

Previously, FDA policy had restricted 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 prescriber'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 (D.C. Cir. 2006)). A three-judge panel of the District of Columbia Court of Appeals reversed and remanded the district court's decision, finding for the plaintiffs. The justices 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 justices 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 the plaintiffs sought in this case because both involve the right of the individual to the "possession and control of his own person . . ." (p. 484).

The three-judge panel's decision was short lived, however. In August 2007, the full D.C. Court of Appeals issued an 8–2 decision reversing the decision (495 F.3d 695, D.C). The majority noted that it was reluctant to create new constitutional rights and that a right to experimental drugs is not a fundamental right deeply rooted in the nation's history and tradition. The court felt that this was an action better left to Congress. The majority also distinguished *Cruzan*, stating that the decision in that case was predicated on a common law rule that forced medical treatment is battery and that there is a long tradition of protecting the patient's decision to refuse unwanted medical treatment. The plaintiffs appealed to the U.S. Supreme Court, but the Court declined to consider the case, thus allowing the court of appeal's decision to stand (552 U.S. 1159 (2008)).

FDA's Expanded Access Program

Although the FDA opposed the plaintiffs' constitutional arguments in court and prevailed, it was sympathetic to their cause, enacting final regulations in August of 2009 that ultimately achieved many of the outcomes the plaintiffs sought

(74 Fed. Reg. 40900). The final regulation created what is known as the "expanded access program" and permits patients with life-threatening diseases or conditions who have exhausted approved treatment options to seek access (through their treating physician) to experimental drugs even in phase 1. It also expands and clarifies the treatment use of experimental drugs. Since the regulation has gone into effect, the FDA stated that it has received numerous questions, prompting it to issue a question-and-answer guidance document in June of 2016 and updated in October of 2017 (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf). This guidance is intended to answer frequent questions from industry, researchers, physicians, IRBs and patients about the FDA's implementation of the 2009 regulations. Another final regulation, also issued in August of 2009, clarifies and establishes the criteria for drug manufacturers to charge patients for investigational drugs (74 Fed. Reg. 40872). Perhaps the biggest obstacle to patients is that the FDA cannot compel drug manufacturers to provide IND drugs and many have refused to provide the drugs because of limited supply, safety concerns because of the limited testing, or fear that an adverse event will ultimately jeopardize the drug's approval (July 2017 GAO report: https://www.gao.gov/products/GAO-17-564).

Right-to-Try Laws

Critics contend that the FDA's expanded access process is too cumbersome and time consuming for the terminally ill, noting that months may transpire before an individual can actually obtain the drug, if at all. In response, the FDA noted that it has approved 99% of the 5,800 applications for IND drug treatment it received between 2012 and 2015, and issued a draft guidance in February of 2015 (80 Fed. Reg. 7318) that was finalized and updated in 2017 (https://www.fda.gov/media/91160/download) with the intent of streamlining the patient application process. Nonetheless, by 2018, approximately 38 states have passed "right-to-try" laws that allow the patient to go directly to the drug manufacturer and bypass the FDA; however, the manufacturer is still not obligated to provide the drug.

In May of 2018, Congress passed a federal right-to-try law amending the FDCA (P.L. No. 115-176). The federal law includes essentially the same provisions as the FDA's policy; however, it creates an alternative pathway to investigational drugs by removing the FDA from the process. For additional information on the federal right-to-try law, one can visit the FDA website at: https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try.

Expedited Approval of Drugs Intended to Treat Serious or 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 if it is intended for the treatment of a serious condition, and that (1) it demonstrates the potential to address unmet medical needs for the condition (FDA designation: Fast Track) or (2) it demonstrates substantial improvement on a clinically significant endpoint compared with available therapies (FDA designation: Breakthrough Therapy).

Approval will be conditioned on the completion of postmarket 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 4 studies do not confirm the drug's safety and effectiveness.

In addition to the authority provided by the FDAMA, other sections of the FDCA permit the FDA to expedite drug approval for drugs intended to treat a serious condition in two other ways: (1) by "accelerated approval," if the drug provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint reasonably likely to predict clinical benefit; or (2) by "priority review," if the drug provides a significant improvement in safety or effectiveness.

Take-Away Points

- The FDA may approve an investigational drug for widespread patient treatment of serious or immediately life-threatening diseases if certain conditions are met.
- The FDA may approve an investigational drug for an individual patient with a serious disease or condition where there is no comparable or satisfactory alternative therapy provided that certain conditions are met.
- Despite FDA efforts to expand access to IND drugs, several states have passed right-to-try laws, believing that the FDA process is too restrictive. More recently, the federal government has also passed a right-to-try law.
- A federal court determined that a patient has no constitutional right to obtain an unapproved drug for treatment.
- The FDA can expedite the approval of a new drug for life-threatening or serious injury if certain conditions are met.

Study Scenarios and Questions

Mentadine (fictional) has just passed phase 1 of the IND process. A terminally ill patient asks you, the pharmacist, if it is legally possible for her to get this drug. Respond to the patient's inquiry.

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 (4 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 and are subject to the FDCA requirements like new drug products, but unlike drugs, biologics 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 the required standards. If a biological product contains a drug, it will be classified as either a biological or a drug, depending on the product's primary mode of action.

Unlike with drugs, the law had not recognized generic biological products until the passage of the ACA in 2010. The healthcare reform law contains a subtitle called the Biologics Price Competition and Innovation Act (BPCIA) intended to create a regulatory framework to facilitate the approval of generic biologics (also called biosimilars or follow-on biologics). The law defines biosimilarity to mean that the biological product is "highly similar" to the reference product with no clinically meaningful differences. The BPCIA grants the FDA the authority to determine whether a biosimilar is therapeutically equivalent to a reference biologic, and thus can be interchanged in the same manner as generic drug products. In order to demonstrate interchangeability, the applicant must establish that the biosimilar can be expected to produce the same clinical results as the reference product without any greater risk. The law grants a 12-year marketing exclusivity period to the reference product. Because of a federal court of appeals decision in 2015, the exclusivity period was actually extended by 6 months, until the U.S. Supreme Court in 2017 overturned the decision (*Sandoz v. Amgen*, 137 S.Ct. 1664 (June 12, 2017)). The ACA requires a biosimilar manufacturer to give notice to the brand name manufacturer 180 days prior to the "first commercial marketing." The court of appeals held that the notice could not be given until after FDA approval. The Supreme Court, however, applied the plain language of the ACA, holding that the notice is based on the marketing date, not the FDA approval date.

Between 2014 and 2017, the FDA has issued several guidance documents addressing its expectations for biosimilar products, including how the FDA interprets the BPCIA, including exclusivity, biosimilarity, and interchangeability; the quality

considerations companies should take into account when attempting to demonstrate biosimilarity to a reference product; the agency's recommended approach for demonstrating biosimilarity; labeling; and considerations in demonstrating interchangeability with a reference product (https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm444891.htm).

In 2014, the FDA electronically published the "Purple Book," which is now available as a searchable database (https://purplebooksearch.fda.gov/). The Purple Book (database) lists biological products, including any biosimiliar and interchangeable biological products licensed by the FDA under the PHSA. (Biologic product substitution is discussed further in another section of this book, "The Orange Book and Generic Substitution.")

Take-Away Points

- Biologics are products derived from living organisms and used for the prevention, treatment, or cure of a disease or condition of humans.
- The FDA must approve biologics prior to marketing; however, they are licensed by the Public Health Service.
- As part of the ACA, the BPCIA allows the FDA to approve biosimilar products.
- Biosimilarity means that the biological product is "highly similar" to the reference product with no clinically meaningful differences.
- For interchangeability, the applicant must establish that the biosimilar can be expected to produce the same clinical results as the reference product without any greater risk.
- The reference biologic is entitled to 12 years of marketing exclusivity.

Study Scenarios and Questions

As a pharmacist is administering a flu vaccination to a patient, the patient asks if the vaccine is considered a drug and approved by the FDA prior to marketing. What would be the correct information for the pharmacist to provide to the patient?

MedWatch Voluntary Reporting Program

The FDA maintains a voluntary reporting system called MedWatch that allows healthcare 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 (Form FDA 3500) can be accessed and completed online at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home. Pharmacists submit a large number of adverse drug reaction reports and also 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 healthcare professionals to furnish the FDA with information about suspected adverse events, product quality problems, and product errors. The FDA encourages practitioners to submit reports, pointing out that a report is neither 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 allows for reporting but also provides a wealth of safety information on products, accessible from its website at http://www.fda.gov/Safety/MedWatch/default.htm.

Pharmacy Requirement to Provide Patients with MedWatch Number

Although the MedWatch program was intended initially for reporting by healthcare professionals, the scope has been broadened by the FDAAA to include patient reporting. The FDAAA required the FDA to implement a dormant 2004 regulation mandating that pharmacies provide patients with notification of a toll-free number so they can report adverse events (73 Fed. Reg. 402, Jan. 3, 2008). As of July 1, 2009, pharmacies must provide patients with the statement: "Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088" (the MedWatch number). Notification to patients must be distributed to patients with each new and refill prescription and may occur by any of the following means:

- On a sticker attached to the container or package
- On a preprinted vial cap
- On a separate sheet of paper
- In patient medication information distributed by the pharmacy
- In a MedGuide

Take-Away Points

- The voluntary MedWatch program allows healthcare professionals as well as the public to report any serious adverse events and other suspected medical product problems directly to the FDA.
- Healthcare professionals have a moral obligation to report to the MedWatch program possible adverse drug events and other possible problems related to products covered under the FDCA.
- Pharmacies have an obligation to notify patients of the MedWatch phone number via five methods.

Study Scenarios and Questions

A patient phones his pharmacist to inform her that he has started having serious problems swallowing, which he believes can be attributed to the drug he was recently prescribed. The pharmacist tells the patient to discontinue the drug and call his prescriber immediately. The patient asks the pharmacist if the FDA should be notified and the pharmacist replies: "No. We can't be absolutely certain the drug caused your problem; and, if it is a recognized adverse event from the drug, I'm sure the FDA already knows about it." Is the pharmacist's response proper and if not, what should the pharmacist have said?

Medical Devices

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 (MDA) (P.L. No. 94-295), 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 another type of action by the FDA.

Pursuant to the Medical Device Amendments, the FDA must classify all devices marketed after 1976 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 the CGMP. 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 before the FDA will permit marketing. 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.

The FDA will not regulate a product as a medical device if it is intended for general wellness, is of low risk, and makes no references to diseases or conditions (General Wellness: Policy for Low Risk Devices final guidance, September 2019, at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM429674.pdf). For example, exercise equipment intended for general physical conditioning would not be a medical device. The same rule generally applies to computer software and mobile applications. The FDA has historically regulated software that it believed met the definition of a device. However, the 21st Century Cures Act of 2016 amended the definition of a device (§520(o)(1)(E)) to exclude certain software functions, prompting the FDA since 2017 to issue numerous guidance documents to provide clarity on the FDA's regulation of digital health products (https://www.fda.gov/MedicalDevices/DigitalHealth/ucm562577.htm). The 21st Century Cures Act also required the FDA to revise its February 2015 guidance for Mobile Medical Applications (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-device-software-functions-and-mobile-medical-applications). In this guidance, the FDA noted that many mobile applications are not medical devices and will not regulate them (e.g., software that actively monitors exercise activity). Then, the FDA provided a list of software functions that may meet the definition of a medical device but that the FDA intends to exercise enforcement discretion as they pose a lower risk to the public. An example in this category would include software that tracks medications and provides user-configured reminders for improved medication adherence. Finally, the FDA provided a list of software functions that are considered medical devices and that the FDA will focus its regulatory oversight on as they pose a risk to a patient's safety if the software were to not function as intended. An example in this category would include a sensor that is connected to a mobile platform to measure and display the electrical signal produced by the heart.

Like 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. Additionally, like drugs, certain devices may be available by both prescription and OTC. While hearing aids required a prescription and medical oversight for a long time, in November of 2022, the FDA issued a final rule to improve access to safe, effective, and affordable hearing aids for millions of Americans (87 Fed. Reg. 50698). This action enabled consumers of 18 years of age and older with perceived mild to moderate hearing loss to purchase hearing aids directly from stores or online retailers without the need for a medical exam, prescription, or a fitting adjustment by an audiologist. The goal was to broaden access to hearing aids without seeing a physician for an exam or an audiologist for help with fitting. At the same time, the FDA also issued a separate guidance document to clarify the differences between hearing aids (prescription and OTC), which are both medical devices and personal sound amplification products, which are not regulated as medical devices but rather consumer electronics that help people with normal hearing amplify sounds in certain environments. The FDA provides additional information and resources on heading aids at https://www.fda.gov/medical-devices/consumer-products/hearing-aids.

Custom devices ordered by healthcare 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 the CGMP and 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 not only benefit 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 healthcare 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 requiring that device-user facilities and distributors must also report to the FDA 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 that is not a physician's office." This law was modified and expanded in 1992 (P.L. 102-300). Subsequently, the FDAMA 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. Through a phased-in system between 2014 and 2020, most medical devices were required to contain a "unique device identifier" (UDI) on its label and packages (78 Fed. Reg. 58786 Sept. 24, 2013). The FDA also administers the Global Unique Device Identification Database (GUDID) which provides a reference catalog for medical devices with a UDI. Most of the information submitted to GUDID is also available to the public through Access GUDID at https://accessgudid.nlm.nih.gov/.

In 2015, the FDA introduced a new, voluntary, expedited approval process known as the Expedited Access Pathway (EAP) for devices that can demonstrate the potential to address unmet medical needs for life-threatening or irreversibly debilitating diseases or conditions and that are subject to premarket approval applications (https://www.federalregister.gov/documents/2015/04/13/2015-08364/expedited-access-for-premarket-approval-and-de-novo-medical-devices-intended-for-unmet-medical-need). The purpose of the EAP program is to help patients have more timely access to these medical devices while providing reasonable assurance of safety and efficacy. Subsequently, the 21st Century Cures Act added the Breakthrough Devices Program for essentially the same types of devices and with essentially the same objectives as the EAP program. The Breakthrough Devices Program supersedes the EAP Program (Breakthrough Devices Program Draft Guidance, October 2017 at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM581664.pdf).

Take-Away Points

- The MDA of 1976 establishes a comprehensive system of device regulation, including device classification, premarket testing, and standards of performance.
- The FDA places all medical devices into one of three classes, with Class III devices requiring premarket approval.
- Devices intended for general wellness, are of low risk, and make no references to diseases or conditions, are not medical devices.
- The 21st Century Cures Act excludes certain software applications from being considered medical devices; however, the FDA has provided a list of software functions that are considered medical devices and that the FDA will focus its regulatory oversight on as they pose a risk to a patient's safety if the software were to not function as intended.
- Some medical devices available to the public are prescription only such as contact lenses and diaphragms.
- Some medical devices may be available to the public by both prescription and OTC, such as hearing aids.
- Custom devices ordered by healthcare professionals are generally exempt from some of the MDA requirements.
- Medical device firms and device-user facilities must report any death or serious injury related to a product.
- The FDA can require medical device firms to perform certain specific actions if it determines that a device presents an unreasonable risk of substantial harm.
- The 21st Century Cures Act created the Breakthrough Devices Program, which superseded its predecessor, the EAP program.

Study Scenarios and Questions

A patient purchasing syringes and needles for insulin injection asked the pharmacist whether the FDA regulates these products and if so, in what manner. Provide a complete response to this patient.

Cosmetics

Sections 601 to 603 of the FDCA and 21 C.F.R. parts 700–740 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 (except for color additives), although manufacturers must substantiate the safety of their cosmetic product and each of its ingredients. Moreover, currently, the manufacturer of a cosmetic does not have to conform to CGMP or even register with the FDA; registration is voluntary. The FDA may, however, take regulatory action against a manufacturer to remove the product 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 the consumer can read them at the point of purchase. This information is especially important to consumers with allergies to certain ingredients. A Cosmetics Labeling Guide is available from the FDA that provides step-by-step help with cosmetic labeling, with examples and answers to questions manufacturers often ask about labeling requirements under U.S. laws and regulations (see https://www.fda.gov/cosmetics/cosmetics-labeling-regulations/cosmetics-labeling-guide#clgl).

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 the average 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. 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 considered 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. Any 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.

In December of 2022, Congress expanded the FDA's regulatory authority over cosmetics in the first major statutory change to the FDCA regarding the regulation of cosmetics since 1938. A summary of a few of the key provisions expected from the Modernization of Cosmetics Regulation Act (MCRA) include:

- **Facility registration and product listing:** Facilities that manufacturer/distribute cosmetics must register (initial within 1 year then biennial) with the FDA and provide a listing of products. Excluded from the definition of facilities includes beauty shops, retailers, hospitals, hotels, research facilities, and establishments that only label, relabel, pack, repack, hold, or distribute.
- **GMPs:** The FDA must issue GMP rules (proposed within two years and final within 3 years) for facilities that ensure cosmetic products are not adulterated and will result in records that demonstrate compliance.
- **Adverse event reporting:** The MCRA requires adverse event reporting within specific timeframes, including serious adverse events (including death, life-threatening experience, inpatient hospitalization, infection, significant disfigurement) no later than 15 business days. Records related to adverse events also must be kept for 6 years.

Additional changes include introduction of safety substantiation for cosmetic products, including record retention; expansion of labeling requirements; expansion on enforcement, mandatory

recalls, recordkeeping, and record inspection; new ingredient-specific requirements for talc-containing cosmetic products; and new requirements to assess the use, safety, and risks of perfluoroalkyl and polyfluoroalkyl substances (PFAS) in cosmetic products. Since the MCRA requires the FDA to develop and issue regulations regarding these changes, it will likely take months to years until these new or expanded standards are proposed and finalized.

Take-Away Points

- Cosmetics do not require premarket approval; however, they are subject to certain misbranding and adulteration laws and the FDA can take regulatory action against them.
- Cosmetics can be misbranded for several reasons.
- Cosmetics can be considered adulterated for many of the same reasons that a drug can be adulterated.
- The Modernization of Cosmetics Regulation Act (MCRA) of 2022 will bring major changes to the cosmetic industry in the near future, including facility registration and product listing requirements, GMP standards, and adverse event reporting requirements.

Study Scenarios and Questions

A patient asks the pharmacist whether the FDA regulates cosmetics and if so, in what manner. How should the pharmacist answer the patient?

Drug Advertising and Promotion

Product advertising and promotion are essential in order to inform and educate the public about new and existing products, and at the same time, are critical to the commercial success of the products. 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. Of particular regulatory concern are communications promoting drugs for off-label use, false and misleading claims, unsupported product comparisons, and overstatements of efficacy or understatements of risk. 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)) and has a special office for this purpose called the Office of Prescription Drug Promotion. The FTC (usually in collaboration with the FDA) regulates nonprescription drug advertising under the FTC 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, consumer protection laws and many states' pharmacy laws prohibit false, misleading, or deceptive advertising.

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, plaintiffs have successfully challenged various aspects of the FDA's regulation of company-sponsored educational symposia and company distribution of off-label use materials. Any future governmental attempts to regulate activities such as direct-to-consumer (DTC) advertising and Internet drug promotion must also pass First Amendment tests.

Prescription Drug Advertising: Manufacturer to Professionals

Pharmaceutical manufacturers promote their products to healthcare 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 healthcare 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 200–202). 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).

There are exceptions to the "true statement" requirement. 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. § 202.1(e)(2)(i)). Reminder ads are not permitted for drugs with black box warnings. 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. Another exemption from the "true statement" is institutional ads, which include only the company's name and area of research but no drug name. Help seeking or disease awareness communications, which discuss a medical condition or disease and may include the company name, but not a drug name, are also exempt.

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 healthcare 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.

Because the brief summary requirement is really quite extensive, manufacturers struggled to include all of the required information in broadcast media advertising such as on television. As a result, prescription drug advertising in broadcast media need only include a summary of major risk information 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 (discussed in the DTC advertising section of this chapter).

Journal Advertising

Even a casual reader of biomedical 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 and was in fact already trying to address. Today, the agency claims that it actively scrutinizes journal advertisements and, when necessary, takes enforcement actions. However, a study by researchers from Mount Sinai School of Medicine concluded that only 18% of journal ads published in 2008 in top U.S. biomedical journals met all FDA requirements and over 50% of the ads failed to quantify serious risks (http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0023336).

Industry-Supported Educational Programs Distinguished from Promotional Programs

For several years, pharmaceutical manufacturers have sponsored and funded educational programs (usually for continuing education credit [CE]) for healthcare professionals. In pharmacy, this sponsorship often is 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 healthcare providers to attend. Those inducements included fees for attendees, rooms and meals at lavish resorts, and free vacations. Some speakers were receiving honoraria of hundreds of thousands of dollars per year. As a result of the congressional investigation, the FDA published the "Final Guidance Statement on Industry-Supported Scientific and Educational Activities" in 1997 (62 Fed. Reg. 64074; https://www.gpo.gov/fdsys/pkg/FR-1997-12-03/pdf/97-31741.pdf), maintaining the FDA's traditional position that scientific and educational activities performed by or on behalf of drug manufacturers are subject to regulation under the FDCA.

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 that the "true statement" requirements apply, including "fair balance," and discussions of off-label uses, then, might trigger FDA scrutiny.

The guidance lists several factors that 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 that 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. 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 (D.C. 2000), arguing that a violation of the guidance does not mean that the conduct was illegal, because 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 and vacated the District Court's decision that the guidance was unconstitutional (*Washington Legal Foundation v. Henney*, 36 F. Supp. 2d 418 (D.C. 1999)).

The DHHS's OIG added its opinion about manufacturer-funded educational activities in a 2003 document titled "OIG Compliance Program Guidance for Pharmaceutical Manufacturers" (68 Fed. Reg. 23731; https://oig.hhs.gov/documents/compliance-guidance/799/050503FRCPGPharmac.pdf). 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 who are 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 anti-kickback statute.

Very aware that the government and the American public perceives the drug industry as ethically challenged in its relations with healthcare professionals, the PhRMA drafted and published a voluntary guide called "Code on Interactions with Healthcare Professionals," first in 2002 and updated in 2009 and revised in August 2021 (effective January 2022) (https://www.phrma.org/codes-and-guidelines/code-on-interactions-with-health-care-professionals). The Code prohibits companies from what used to be a common practice of providing entertainment and recreational activities to healthcare professionals, either separate from or in conjunction with an informational or educational program. Companies may provide financial support for CE programs but only through a CE provider and the company may not provide advice or guidance to the CE provider. Although the company should not provide meals directly, the CE provider may choose to do so from the financial support provided to it from the company. Speaker expenses and honorariums are to be paid by the CE provider. The Code also prohibits providing healthcare professionals, either directly or at programs, with items, even of minimal value, such as pens, note pads, mugs, or even stethoscopes that do not advance education.

Physician Payment Sunshine Act

The latest iteration related to preventing manufacturers from exerting undue influence over at least some healthcare professionals is the Physician Payment Sunshine Act that was included in the ACA of 2010. CMS enacted final regulations in 2013 to implement the law (78 Fed. Reg. 9457) and modified them in November 2014 (79 Fed. Reg. 67547). The Physician Payment Sunshine Act and regulations mandate disclosure by drug and device manufacturers and group purchasing organizations to the DHHS of nontrivial payments to physicians and teaching hospitals. The CMS is then responsible for posting this information on a public website. Reportable payments include entertainment, gifts, meals, travel, consulting fees, speaking fees and certain research funding. Because the website lists the names of physicians and the amount of payments they receive, physicians are especially concerned about how the public will interpret these data.

FDA's Bad Ad Program

In 2010, the FDA implemented the "Bad Ad Program," with the intent of enlisting healthcare professionals to help ensure that company promotion of prescription drugs is truthful (https://www.fda.gov/drugs/office-prescription-drug-promotion/bad-ad-program). The FDA noted that its ability to monitor promotional activities in settings such as prescriber's offices, at local dinner programs, and at promotional speaker programs is limited. Thus, the agency asks healthcare professionals to assist it by recognizing misleading promotional activities and reporting them either by phone (855-RX-BADAD) or by email (badad@fda.gov). One year after the program's implementation, the FDA announced that complaints against drug companies tripled. Building on the success of the program, the FDA developed a web-based program called EthicAd to educate consumers about misleading DTC ads (https://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/default.htm).

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 benefits 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 healthcare, 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 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 final guidance in August 1999 (64 Fed. Reg. 43197). Of particular importance, the FDA clarified what would satisfy the "adequate provision" requirement for DTC advertising through broadcast media. Advertisers may provide a summary of major risks (termed as the "major statement") 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 healthcare provider. The FDA suggests that manufacturers should use all four sources of information. Although the regulations require that the approved product labeling (package insert) be disseminated in connection with broadcast advertisements, the FDA has instead asked manufacturers to consider translating the required information into language comprehensible to the general public.

In August of 2017, the FDA issued a notice in the *Federal Register* that there is concern as to whether the "major statement" is fulfilling its purpose (82 Fed. Reg. 39598). The FDA noted that some believe that risk information is too long, resulting in reduced consumer comprehension and minimization of important risk information, while others believe the ads do not include adequate risk information or that they leave out important information. The FDA announced that it was exploring the usefulness of limiting the risks in the major statement to those who are severe, serious, or actionable. This would be coupled with a disclosure that not all risks are included in the ad. The FDA asked for public comments on the content of risk information.

Regarding DTC print advertising, the FDA announced in a 2004 draft guidance (revised in August 2015 80 fed reg 46990 August 2015) that it does not intend to hold manufacturers to the "brief summary" requirement, but rather to what it calls a "consumer brief summary." The FDA feels the level of information required for a "brief summary" is not appropriate or useful for patients (see 80 Fed. Reg. 46990). 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: by using a modification of FDA-approved patient labeling, such as patient package inserts, or MedGuides, if available.

Just as the FDA scrutinizes advertising directed to healthcare professionals, it also evaluates advertising directed to consumers and has taken enforcement actions when it deems it necessary. However, in November of 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* (https://www.gao.gov/products/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 of this material, the GAO could find no documented criteria for prioritization. The report noted that informal criteria being used by FDA reviewers are 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, the agency issues fewer letters, and that the effectiveness of the letters is limited. A follow-up report by the GAO published in 2008 did not find much improvement (http://www.gao.gov/products/GAO-08-758T).

The FDAAA provided the FDA with additional authority over DTC in 2007 by allowing it to require a prereview of DTC ads. Because the First Amendment precludes censorship, the FDA's authority after prereview is limited to providing recommendations to the company. The FDA may, however, require a change in an ad if the change addresses serious risks associated with the drug's use (see FDA draft guidance at https://www.fda.gov/media/82590/download).

In recent years, the FDA has been concerned about distracting ads, both print and broadcast, which divert the consumer's attention from the drug's risks. The FDA issued a draft guidance in May of 2009 to advise the drug industry of the agency's expectations regarding how risk information should be presented (*Presenting Risk Information in Prescription Drug and Medical Device Promotion*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf). The FDA warned advertisers about busy scenes, frequent scene changes, and speeding up of an announcer's description of risks as detracting from the consumer's comprehension. As one example, the FDA gave a TV ad for a cholesterol-lowering drug that contains factually accurate risk information but is accompanied by loud upbeat music and quick scene changes showing comforting visual images of patients benefiting from the drug. The guidance indicates that the FDA will look at the "net impression" that the ad conveys from the perspective of a reasonable consumer.

Ultimately, the courts may have a significant influence on the type of information a company must provide to consumers. A New Jersey superior court 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 healthcare professional, not the consumer.

Promoting Prescription Drugs and Devices Through Social Media

The FDASIA of 2012 mandated the FDA to issue guidance on promotion through social media by July of 2014, and the FDA complied with multiple draft guidance documents. The first draft guidance, published in January of 2014, addresses "interactive promotional media," defined as technologies that often allow for real-time communications and interactions such as some websites, Twitter, Facebook, live podcasts, and firm blogs (https://www.fda.gov/downloads/drugs/guidances/ucm381352.pdf). The guidance states that the FDA's regulatory authority extends both to product promotional communications carried out by the company as well as conducted by someone else on the company's behalf. In determining whether the company is accountable for a communication, the FDA will examine whether the company or anyone acting on its behalf is influencing or controlling the activity in whole or in part. In most accountable situations, the company is required to submit all promotional labeling and advertising pieces to the FDA at the time of initial dissemination.

The FDA published two additional guidance documents in June of 2014. One provides guidance on using social media platforms with space limitations such as Twitter (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401087.pdf). The clear message is that any communication must have fair balance conveying both benefits and risks in a balanced manner, even though space limitations may pose challenges. The company should provide a mechanism to allow direct access to a more complete discussion of the product's risks. If fair balance cannot be achieved for a specific product, such as those with complex indications or serious risks, the company should reconsider using that platform.

The other guidance focuses on how manufacturers should respond, if they choose to do so, to correct third-party misinformation about their product on the Internet or through social media, regardless of whether it appears on the company's or a third party's site (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401079.pdf). Misinformation is defined as positive or negative incorrect information about the product disseminated by a third party not under the company's control or influence and that is not produced by or on behalf of or prompted by the company in any way. The FDA states that if a

firm corrects misinformation in a truthful and non-misleading manner, pursuant to the requirements established in the guidance, the FDA will not object, even if the company does not satisfy the otherwise applicable regulatory requirements related to labeling or advertising.

Promoting Prescription Drugs and Devices for Off-Label Uses

Many of the most serious advertising violations and penalties generally involve promotions of drugs for off-label uses (also termed unapproved or unlabeled uses). The term, "*off-label use*" refers to indications other than those approved by the FDA, and thus, are not included in the approved labeling. The FDA historically has been concerned that adverse health consequences could result if healthcare 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 had 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 healthcare practitioner (guidance published at 61 Fed. Reg. 52800 (1996)). In stark contrast, the FDA recognizes that healthcare professionals commonly prescribe and dispense drugs for off-label use and has endorsed this practice as legal under the FDCA. (This issue will be discussed in more detail elsewhere.) This dichotomy created a dilemma in that prescribers and dispensers are entitled to access to off-label use information, yet manufacturers were denied the right to supply any information.

The FDAMA (§ 551 and § 552) mitigated the dilemma somewhat by relaxing FDA policy to allow companies to provide written information about off-label uses under certain conditions to healthcare professionals and certain entities such as pharmacy benefit managers, health insurance plans, and group health plans. The written information had to 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. The conditions for disseminating this information included that the company must (1) have filed an application for approval for the use, (2) submit to the agency 60 days before dissemination of 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 were ruled unconstitutional on First Amendment grounds by the *Washington Legal Foundation v. Friedman* and *Washington Legal Foundation v. Henney* cases (mentioned earlier). However, the court of appeals allowed the provisions to remain after the FDA changed its position to assert that the FDAMA provisions were not requirements but merely established a "safe harbor."

The FDAMA provisions related to off-label use dissemination, however, expired on September 30, 2006, prompting the FDA to issue a final guidance in January of 2009 regarding the distribution of medical and scientific journal articles and reference publications for educational purposes. The FDA emphasized in the guidance that, in the interest of public health, it is important that healthcare professionals be able to receive truthful and non-misleading publications on unapproved new uses. The FDA also continued to recognize that this information is not a substitute for the FDA premarket review process, which allows the FDA to be proactive in protecting the public from unsafe or ineffective medical products (see https://www.fda.gov/media/88031/download). The guidance essentially incorporated the provisions of FDAMA, minus the requirements that the company must have filed an NDA for the use or have submitted a copy of the article and related clinical information to the FDA 60 days prior to dissemination, because these restrictions would likely violate the First Amendment. The FDA emphasized that the scientific and medical information must not be false or misleading, not pose a significant risk to the public if relied upon, and be separated from promotional materials.

However, a 2012 landmark court decision, *United States v. Caronia*, 703 F.3d 149 (2nd Cir. 2012), discussed in the case studies section of this chapter, forced the FDA to reevaluate its position on off-label use dissemination. In *Caronia*, the court reversed a pharmaceutical sale representative's criminal conviction for orally promoting off-label uses of a drug to physicians. The court held that truthful and non–misleading statements regarding off-label use promotion for a lawful purpose are protected under the First Amendment.

Most likely in response to *Caronia*, the FDA issued a 2014 revision draft of the 2009 guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf). The 2014 revision draft guidance

does not discuss oral statements or make any mention of *Caronia*. Rather, it clarifies the FDA's position on the dissemination of written information. The revision broadens what the FDA considered acceptable information for dissemination in the 2009 guidance and categorized three types of acceptable scientific and medical information that may be distributed: (1) scientific or medical journal articles; (2) scientific or medical reference texts, in their entirety or as individual chapters; and (3) clinical practice guidelines. For each type of information, the guidance lists several specific requirements that must be met by the distributor, if it wishes to stay in a "safe harbor."

Subsequently; however, in 2015, the FDA found itself on the losing end of yet another first amendment lawsuit over off-label uses (*Amarin Pharma, Inc. v. FDA*, 119 F.Supp.3d 196 (N.Y.D.C.S.D Aug. 7, 2015)). In *Amarin*, the federal district court, relying on *Caronia*, ruled against the FDA to allow the company to engage in truthful and non–misleading "promotion" of off-label use information to healthcare professionals. Prior to *Amarin*, the FDA held the opinion that *Caronia* narrowly applied to criminal convictions and not to a misbranding action for off-label promotions. The parties agreed to settle the case in March of 2016.

The *Amarin* decision, together with other First Amendment lawsuits, triggered an outcry for the FDA to clarify its policy on the promotion of medical products for off-label uses. The FDA responded with two draft guidance documents in June of 2018. The first guidance addresses communications to healthcare providers, titled "Medical Product Communications That Are Consistent with the FDA-Required Labeling-Questions and Answers" (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf). However, the guidance only addresses communications about approved uses of a medical product that are consistent with but not included in the FDA-required labeling. It does not address the issues in *Caronia* and *Amarin* regarding the truthful and non–misleading promotion of an off-label use. The guidance establishes a three-factor test that the FDA will use to determine if promotional communications are consistent with required labeling: (1) Does the information in the communication differ from or conflict with the information about conditions of use in the required labeling? (2) Will the information in the communication increase the potential for harm to health compared with the required labeling? (3) Do the directions for use in the FDA-required labeling allow the product to be used safely and effectively under the conditions discussed in the communication?

The second guidance addresses communications of HCEI to such entities as payors and formulary committees (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537347.pdf). Remember that the misbranding provision of the FDCA (§502(a)) provides that HCEI cannot be false or misleading in any particular. The guidance provides some clarity on this misbranding provision, including what information qualifies as HCEI; who is the appropriate audience; when does information relate to an approved indication; what is the required level of evidentiary support; and what documents should accompany HCEI.

Then, in 2021, the FDA published its final "intended use" rule and amended its regulations describing the types of evidence it would consider in determining whether a company intended to market a prescription drug or medical device for a use that the FDA has not approved (86 Fed. Reg. 41383). The final rule helped clarify that the FDA will not make a determination about a company's intent regarding off-label use based solely on knowledge that its product is being prescribed and used off-label. Furthermore, the FDA will evaluate the question of whether a company has expressed an intended use that is off-label on a case-by-case basis, and that it will consider a wide range of evidence in determining intended use.

However, it is also important to consider that there are times that manufacturers may receive unsolicited requests for off-label information about their products. To help address these situations, the FDA issued draft guidance in 2011 to show manufacturers how they should respond to unsolicited requests for off-label information, including both requests made privately and requests made in public forums, including electronic media (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf). For individual private requests such as by email or telephone, the FDA stated that a manufacturer can provide off-label information only to the individual making the request and that the answer should be no broader than the question asked. For public, unsolicited requests through electronic media such as websites, discussion boards, and chat rooms, the guidance provides that the manufacturer may provide only contact information and not off-label information. The manufacturer may then provide off-label information only to those individuals who contact them directly. The FDA chose this approach out of concern for individuals who did not

request the information and, because of the enduring nature of online responses, in light of the fact that the information might become outdated.

Nonprescription Drug Advertising by Manufacturers

As noted earlier, the FTC regulates nonprescription drug advertising under the FTC Act. The FTC Act allows the FTC to prohibit unfair methods of competition, 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 FTC 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 FTC'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 broadcasted 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 that 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 FTC Act has a more important role in protecting the consumer against false and misleading advertising.

Take-Away Points

- The FDA regulates prescription medical product advertising, while the FTC regulates nonprescription drug advertising.
- Government regulation of commercial (advertising and promotion) speech is subject to constraint under the First Amendment and must meet the four factors articulated in the *Central Hudson* case.
- Advertising and promotion, with certain exceptions, must conform to the true statement requirements of Section 502(n) and the regulations.
- Reminder, institutional, and help-seeking or disease-awareness ads are exempt from the true statement requirement.
- The true statement requirement is violated if the advertising is false or misleading, does not provide "fair balance," or fails to reveal material facts.
- Brochures, booklets, mailings, bulletins, calendars, price lists, and other information disseminated by the manufacturer for use by healthcare professionals is labeling, not advertising.
- The FDA regulates scientific and educational activities performed by or on behalf of drug manufacturers; however, the agency will not regulate the activity if it is independent and nonpromotional, a determination of which requires the evaluation of several factors.
- The Physician Payment Sunshine Act requires that medical product manufacturers disclose nontrivial payments to prescribers and teaching hospitals.

- The intent of the FDA's "Bad Ad Program" is to enlist healthcare professionals to monitor and report on misleading promotional drug manufacturer activities.
- DTC advertising is technically subject to the true statement requirements; however, the agency has urged manufacturers to use language that ordinary consumers can understand, even for print advertising.
- The FDA permits broadcast media advertising to vary from the extensive "brief summary" requirement, provided that the advertiser makes "adequate provisions" for the dissemination of the package insert from one or more of four sources.
- The FDA permits print media advertising to adapt to a "consumer brief summary" rather than a full "brief summary."
- The FDA has historically monitored and regulated distracting ads in both print and broadcast media.
- The FDA regulates communications on Internet and social media sites that are in any manner under the control or influence of the manufacturer; and it requires fair balance on communications on social media platforms with space limitations.
- Historically, the FDA prohibited any dissemination of off-label use information by manufacturers despite the fact that healthcare professionals commonly prescribe and dispense medical products for off-label uses, and this practice is legal.
- The FDAMA allowed companies to provide written information about off-label uses subject to certain requirements. When the FDAMA provisions expired, the FDA continued to allow the practice in a 2009 guidance document, which was revised in 2014 to allow the dissemination of journal articles, reference texts, and clinical practice guidelines, all subject to specific requirements.
- First-amendment lawsuits challenging the FDA's restrictive policy of off-label use promotion have held that the FDA cannot prohibit off-label promotional statements that are truthful and non–misleading.
- The FDA has issued guidance documents providing instruction regarding communications about approved uses of a medical product that are consistent with, but not included in, FDA-required labeling, and communications about HCEI to payors and formulary committees.
- In an FDA final rule, it clarified it would not make a determination about a company's intent regarding off-label use based solely on knowledge that its product is being prescribed and used off-label, and that it would evaluate the question of whether a company has expressed an intended use that is off-label on a case-by-case basis.
- The FTC regulates nonprescription drug advertising under the FTC Act, which prohibits unfair or deceptive acts or practices. The FTC has the authority to order companies to cease and desist, issue corrective advertising, and make affirmative disclosures.
- The Lanham Trademark Act allows for private causes of action for false advertising situations.

Study Scenarios and Questions

1. You are the only pharmacist at a meeting with other healthcare professionals. A physician brings up the topic of DTC 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 CE programs. The company told Dr. Mabel it would pay her $2,000 per one-hour program and would give her the slides to use. Dr. Mabel agreed, and Xecor sponsored a CE program at a local restaurant and personally invited 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 to Dr. 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 Dr. Mabel have committed?

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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 also would 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 a 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 Section 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 Section 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 obviously 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 earlier, 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 animals." 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 that the difference between part B of the drug definition and part C is 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 commonsense 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 many infants were 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 that 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 of 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 of 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 of 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 also were convicted of misbranding E-Ferol on several counts, including that the labeling omitted material facts, failed to bear adequate directions for use, failed to bear adequate warnings, 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 testing and continued to do so even after the adverse incident reports.

Madison and two other defendants pleaded 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 actively 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 a 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 suggested that it was lawful under the FDCA to market a new drug without an approved NDA. It simply established 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 market certain new drugs without an approved NDA, it certainly could not have been read as making such action 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 applied only 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.

Case 2-3 *United States v. Rutherford*, 442 U.S. 544 (1979)

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 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 remarketing 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 it 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 deprecate 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 that are not safe and effective when they are going to die anyway. The government's restriction appears more reasonable when considering that patients might forgo legitimate treatments that might be effective for worthless cures, from which unscrupulous individuals would benefit at the expense of the helpless and desperate. However, some First Amendment advocates would respond 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, 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 to 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.

Case 2-4 *United States v. Caronia*, 703 F.3d 149 (2nd Cir. 2012)

Issue

Whether the criminal conviction of a sales representative for promoting a drug for off-label uses violates his First Amendment rights of free speech.

Overview

As noted in the advertising and promotions section of this chapter, the First Amendment is a significant factor in any government attempt to regulate in this area. Since the late 1990s, the FDA has been successfully challenged for various First Amendment violations. In this case, the FDA attempted to enforce its longstanding policy of preventing the marketing of an approved drug for off-label uses. Opinions by legal scholars regarding the importance of the *Caronia* decision have ranged from a landmark decision to a decision that affirms free speech principles, to a decision that undermines the integrity of the FDCA's regulatory process, to a decision that will not significantly affect FDA enforcement activities.

As you read this case, consider: Is the FDA regulating Caronia's speech or merely using his speech to establish his intent to promote the drug for off-label uses? Is this a distinction that should have any meaning? Does the *Caronia* decision mean that the FDA could not prevent manufacturers or their representatives from making any

claims they want about their products? Will manufacturers still have an incentive to seek FDA approval for off-label uses? Are the alternative means of regulation advanced by the majority realistic?

The court related the facts of this case as:

Orphan Medical, Inc. (now Jazz Pharmaceutical) manufactures Xyrem (gamma-hydroxybutryate) approved for the treatment of patients suffering cataplexy caused by narcolepsy. Because of safety concerns, the FDA allows distribution of the drug nationally through only one centralized Missouri pharmacy. Orphan hired Caronia to promote Xyrem and his salary was based on his sales. Caronia formed a speaker program for Xyrem that enlisted physicians, for pay, to speak about the benefits of the drug. Orphan also hired a physician to promote Xyrem through its speaker programs. The government investigated Orphan and Gleason and on two occasions audio-recorded them promoting Xyrem for unapproved indications such as insomnia, fibromyalgia, restless leg syndrome, chronic pain, and Parkinson's disease.

A grand jury indicted Caronia on both conspiracy to introduce and introducing a misbranded drug into interstate commerce on the basis that Caronia knew the off-label indications he promoted lacked adequate directions for use or adequate warnings. Caronia moved to dismiss the charges at trial, arguing that the application of the FDCA's misbranding provisions to his off-label promotional statements violated his right of free speech under the First Amendment. The FDA countered that it was prosecuting Caronia for his unlawful conduct of misbranding and conspiracy to misbrand, not for his promotional speech. The court rejected the FDA's argument, finding that the FDA was regulating his speech, but that the regulation was lawful and not in violation of the First Amendment, thus convicting Caronia on the misbranding violations.

After discussing the facts and trial court decision, the three-judge panel of the court of appeals rendered its analysis starting with whether the FDA was regulating speech:

> While the FDCA makes it a crime to misbrand or conspire to misbrand a drug, the statute and its accompanying regulations do not expressly prohibit or criminalize off-label promotion. Rather, the FDCA and FDA regulations reference "promotion" only as evidence of a drug's intended use.
>
> Thus, under the principle of constitutional avoidance, we construe the FDCA as not criminalizing the simple promotion of a drug's off-label use because such a construction would raise First Amendment concerns. Because we conclude from the record in this case that the government prosecuted Caronia for mere off-label promotion and the district court instructed the jury that it could convict on that theory, we vacate the judgment of conviction.

The FDA repeated its argument that this case did not invoke the First Amendment because Caronia was not prosecuted for his speech. Rather, his statements were used merely as evidence of the off-label intended use of Xyrem, and that evidence of intent based on verbal statements is admissible without violating the First Amendment. The court responded:

> We begin by addressing the government's contention that Caronia's off-label promotion was used only as evidence of intent in this case. Finding the government's argument unpersuasive, we turn to the principal question on appeal: whether the government's prosecution of Caronia under the FDCA only for promoting an FDA-approved drug for off-label use was constitutionally permissible.

In the course of its analysis, the court took particular note of the U.S. Supreme Court decision the year before in *Sorrell v. IMS Health Inc*., 131 S. Ct. 2653 (2011). In *Sorrell*, a Vermont law prohibited pharmaceutical companies from using prescriber-identifying information for marketing purposes. The Court struck down the law holding that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the First Amendment. . . ." The majority in *Caronia*, based on the Supreme Court's analysis in *Sorrell*, concluded that the FDA's ban of off-label promotion was both "content-based" (because it allowed on-label promotion but banned off-label promotion), and "speaker-based" (because it applied only to pharmaceutical companies, not healthcare providers). Because of this, concluded the court, the FDA's interpretation of the misbranding provisions is subject to "heightened scrutiny." Moreover, concluded the court, the criminal prohibition of off-label promotion fails the even less-rigorous test under the *Central Hudson* decision. (*Central Hudson* is discussed in the text under "The First Amendment to the U.S. Constitution.") The court then proceeded to apply the four prongs of *Central Hudson*.

> The first two prongs of *Central Hudson* are easily satisfied here. First, promoting off-label drug use concerns lawful activity (off-label drug use), and the promotion of off-label drug use is not in and of itself false or misleading. Second, the government's asserted interests in drug safety and public health are substantial. Specifically, the government asserts an interest in preserving the effectiveness and integrity of the FDCA's drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs. ("[O]ne of the [FDCA's] core objectives is to ensure that any product regulated by the FDA is 'safe' and 'effective' for its intended use.")

The court then turned its attention to the third prong of *Central Hudson* that requires that the regulation directly advance the government's interests. Finding that the regulation failed this prong, the court focused on the fact that the FDA drug approval process contemplates that approved drugs will be used for off-label purposes. Even if

pharmaceutical manufacturers are barred from off-label promotion, physicians can prescribe and patients can use the drugs off-label. Stated the court:

> As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs.

The court went on to remark that prohibiting off-label promotion "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information," interfering with "informed and intelligent treatment decisions." To bolster its conclusion, the court pointed to the FDA's guidance document permitting the dissemination of off-label information through scientific journals as well as a statement from the FDA that "public health can be served when healthcare professionals receive truthful and non-misleading scientific and medical information on unapproved uses" of approved drugs.

The court also found that the FDA violated the fourth prong of *Central Hudson*—that the restriction be narrowly drawn to further the interests served.

> Here, the government's construction of the FDCA to impose a complete and criminal ban on off-label promotion by pharmaceutical manufacturers is more extensive than necessary to achieve the government's substantial interests. Numerous, less speech-restrictive alternatives are available, as are non-criminal penalties.
>
> To advance the integrity of the FDA's drug approval process and increase the safety of off-label drug use, the government could pursue several alternatives without excessive First Amendment restrictions. For example, if the government is concerned about the use of drugs off-label, it could more directly address the issue. If the government is concerned that off-label promotion may mislead physicians, it could guide physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information. The government could develop its warning or disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs. The government could require pharmaceutical manufacturers to list all applicable or intended indications when they first apply for FDA approval, enabling physicians, the government, and patients to track a drug's development. To minimize off-label use, or manufacturer evasion of the approval process for such use, the government could create other limits, including ceilings or caps on off-label prescriptions. The FDA could further remind physicians and manufacturers of, and even perhaps further regulate, the legal liability surrounding off-label promotion and treatment decisions. Finally, where off-label drug use is exceptionally concerning, the government could prohibit the off-label use altogether.

The court vacated Caronia's conviction and remanded the case to the district court.

Notes on United States v. Caronia

1. The dissenting judge of the three-judge panel strongly disagreed with the majority on all points, writing an opinion almost as lengthy as that of the majority. Beginning with the issue of intended use, she noted that determining a product's intended use has long been a central concern of food and drug law and is critical to determining whether a product is a drug or not. She pointed to an FDA regulation that provides that intent can be proved from conduct and statements of persons (or their representatives) responsible for labeling the drug. Furthermore, she noted that the First Amendment does not prohibit using speech to prove intent or motive. Thus, she disagreed that the FDA was punishing Caronia for his speech and stated: "I also fail to see how the majority's reasoning would ever allow such speech to support a conviction. For this reason, I conclude the majority's opinion is fundamentally at odds . . . with the underlying premises behind much of the FDCA's regulatory scheme."

   Distinguishing *Sorell*, the judge remarked that the Vermont law targeted speech directly. In Caronia's case, she continued, the speech was merely used as evidence of the drug's intended use. Even if it could be construed that the FDA was regulating speech, she argued, the agency easily met the *Central Hudson* standards. The FDA's action directly advances a substantial government interest, she contended, because proof of a drug's safety for use is a central feature of the FDCA. If manufacturers were allowed to promote approved drugs for unapproved uses, they would have little incentive to prove safety and efficacy for those uses through the NDA approval process. The judge challenged the majority's opinion that the off-label prohibition was speaker-class based. It could not be applied more broadly, she remarked, because drug manufacturers are "the precise group that the government must encourage to participate in the new drug approval process." She also felt that the prohibition against off-label promotion was narrowly drawn, meeting the fourth prong of *Central Hudson*, and felt that the alternative advanced by the majority would not be as effective.
2. The majority advanced a number of alternative ways that the FDA could restrict off-label promotion without being so intrusive. Reading those proposed alternatives, one has to question whether the justices gave any thought to the practicality of implementing those alternatives. Guiding physicians and patients to differentiate misleading promotions, exaggerations, and embellishments from truthful information would likely prove difficult because they would need considerable information about each drug. It would seem this is the service

they currently rely on the FDA to perform. Setting ceilings or caps on off-label prescriptions seem completely unworkable and would likely lead to more lawsuits. Prohibiting off-label use altogether would seem to be an even greater First Amendment intrusion.

3. The implications of the *Caronia* decision are unclear. The decision is applicable only in the second circuit, and the FDA may choose to ignore the decision in other circuits. The FDA decided not to appeal *Caronia* to the Supreme Court and, at least publicly, has commented that the decision will not affect its enforcement of off-label use promotion. Indeed, the multimillion and multibillion dollar off-label promotion case settlements have involved much more than one sales representative. In most of those cases, the promotional efforts include company-wide marketing plans, sales force training programs, and live company programs presented to prescribers. Those cases have also involved false and misleading promotional activities by the manufacturers. The majority opinion emphasized that the First Amendment does not protect false or misleading speech.