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

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

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

HISTORICAL OVERVIEW OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

In order to protect public health, governments of nearly every civilization have sought to protect the public from adulterated food products. More modern laws in the United States in the 1800s against the adulteration of foods and drugs were led by two factors: one, advances in analytical chemistry and microscope technology, and two, studies showing the impact of adulterated foods and drugs on human life. One such study in 1850 showed that average life expectancy actually decreased by as many as 7 years over certain periods of time in Boston and New York in part because of adulterated drugs and foods. (See Hyman, 2002, Chapter 2.)

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

PURE FOOD AND DRUG ACT OF 1906

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

The Court ruled that the misbranding provision in the law prevented false statements only as to the drug's identity (i.e., strength, quality, and purity).

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

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

Food, Drug, and Cosmetic Act of 1938

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

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

In 1948, the extent of the FDCA's jurisdiction was challenged in United States v. Sullivan, 332 U.S. 689, which was discussed in Chapter 1. The defendant pharmacist contended that federal law did not apply to his acts because his acts only affected intrastate transactions. The 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.

DurhamHumphrey Amendment of 1951

The 1938 FDCA required all drugs to be labeled with "adequate directions for use." When the act was passed, however, many drugs on the market were not safe for use except under medical supervision. These drugs could not meet the "adequate directions for use" requirement. The Durham-Humphrey Amendment (also often referred to as

the Prescription Drug Amendment) was enacted in 1951 (65 Stat. 648) to solve this problem. The amendment established two classes of drugs, prescription and over the counter, and provided that the labels of prescription drugs need not contain "adequate directions for use" so long as they contain the legend, "Caution: Federal law prohibits dispensing without a prescription." When dispensed by a pharmacist, inclusion on the label of directions from the prescriber satisfies the "adequate directions for use" requirement.

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

Food Additives Amendment of 1958

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

Color Additive Amendments of 1960

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

STUDY SCENARIO

Compoundit Pharmacy is near a clinic with three dermatologists, and as a result receives several prescriptions a week for various topical prescription ointments, creams, and gels. Most of the ointments, creams, and gels are available commercially, but Compoundit prefers to compound them because of the greater profits. Compoundit makes about a week's supply of the various topical drugs at a time. Other pharmacies in the area also get prescriptions for these topicals, but dispense the commercially made products. Compoundit approached these pharmacies, offering to make and sell them the topicals at a less expensive price than they pay from the manufacturers. The pharmacies agreed to purchase the products from Compoundit.

The FDA and board of pharmacy launch an investigation of Compoundit. Analyze and discuss each of the activities presented in this scenario and whether each activity constitutes compounding or manufacturing.

Kefauver-Harris Amendment of 1962

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

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

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

Medical Device Amendments of 1976

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

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

Orphan Drug Act of 1983

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

Drug Price Competition and Patent Term Restoration Act of 1984

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

THE FOOD AND DRUG ADMINISTRATION (FDA)

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

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

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

Each center has a director and several managers. The field is divided into six geographic regions with 20 district offices. The district offices provide inspections and work coopera-

TABLE 2-1 Examples of Pharmacy Management Career Opportunities

Setting	Managerial Role
Academia	Director of experiential education Coordinator of pharmaceutical care skills lab Director of student admissions Director of graduate studies Chair/vice chair of a division Assistant/associate dean Dean
Association management	Manager Senior manager Associate director Director Senior director Vice president Senior vice president Chief financial officer/chief operating officer Chief executive officer
Community pharmacy	Store pharmacist Pharmacy manager Manager of clinical programs District manager Regional manager Vice president Store owner

TABLE 2-1 Examples of Pharmacy Management Career Opportunities (cont.)

Federal government	Chief of regulatory affairs Deputy chief, Centers for Disease Control and Prevention Drug Service Clinical reviewer Health scientist Research support officer
Health system	Clinical pharmacist Operations pharmacist Residency program director Clinical coordinator Operations manager Assistant/associate director Director of pharmacy Chief pharmacy officer Corporate director of pharmacy Vice president of pharmacy
Home health care	Pharmacy manager
Long-term care	Consultant pharmacist Pharmacy manager
Managed care	Pharmacist/clinical pharmacist Pharmacist manager
Nuclear pharmacy	Nuclear pharmacist Pharmacy manager
Pharmaceutical industry	Sales manager Medical writer coordinator Medical science liaison Marketing manager Research study coordinator District manager Regional manager Director Vice president

Sources: Data from American Pharmacists Association (APhA). Career option profiles. Available at: http://www.pharmacist.com/AM/Template.cfm?Section=Pathways_Program&Template=/CM/ContentDisplay.cfm&ContentID=12183. Accessed November 18, 2011; and Schommer JC, Brown LM, Sogol EM. Work profiles identified from the 2007 Pharmacist and Pharmaceutical Scientist Career Pathway Profile Survey. *Am J Pharm Educ* 2008;72(1) Article 2.

tively with state and local agencies and provide source information to headquarters.

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

Although the FDA is staffed with considerable scientific expertise, it also regularly relies on advice from outside experts in the form of standing advisory committees. Most members of these committees are physicians, but they also include nurses, pharmacists, statisticians,

epidemiologists, and other professionals. Members are recruited through the Federal Register, and often are nominated by professional organizations and professional schools. The secretary of DHHS makes the final selection of members from the list of nominees. Committee size ranges from 9 to 15 members. Although the FDA is not obligated to follow a committee recommendation, it often does.

DEFINING AND DISTINGUISHING DRUGS FROM FOODS, DIETARY SUPPLEMENTS, DEVICES, AND COSMETICS

THE LAW

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

> (f) The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article. (§ 201(f); 21 U.S.C. § 321(f))
>
> (g) (1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of 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).
>
> (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).

Dietary Supplements Versus Drugs

Essentially, DSHEA mandates that the FDA regulate dietary supplements more as a special type of food than as drugs. The FDA cannot require premarket approval of dietary supplements as they do for drugs. Thus, the manufacturer is responsible for determining if its product is safe and that its claims about the product are substantiated by adequate evidence. Moreover, except for new dietary supplements, the manufacturer does not have to provide the FDA with the evidence upon which it relies to substantiate the product's safety and efficacy. DSHEA generally prohibits the FDA from regulating dietary supplements as food additives as well. Since 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. 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
4. Statements describing the general well-being from consumption of a nutrient or

dietary ingredient (e.g., "energizer," "relaxant," "muscle enhancement")

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

Official Compendia

The HPUS defines *homeopathy* as the "art and science of healing the sick by using substances capable of causing the same symptoms, syndromes, and conditions when administered to healthy people."

The 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" (www.homeopathicdoctor.com). The standards for the homeopathy products contained in the HPUS are established by the Homeopathic Pharmacopoeia Convention of the United States (HPCUS). This is a private, nonprofit organization of scientific experts in homeopathy. Because of the recent resurgence of homeopathy and a resultant need for continuous updates, HPCUS has republished the HPUS since 1988 as the HPUS Revision Service, a loose-leaf binder publication that allows for continual revisions without the need to reprint an entirely new volume.

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

PROHIBITED ACTS, PENALTIES, AND ENFORCEMENT

Prohibited Acts: The Law

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

> (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.
>
> (b) The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce.
>
> (c) The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.
>
> (d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 404 or 505.
>
> (e) The refusal to permit access to or copying of any record as required . . . or the failure to

STUDY SCENARIOS AND QUESTIONS

1. A company manufactures and markets capsules filled with pulverized sheep bone. It promotes the product as a treatment for anemia and various blood disorders. Explain whether this product is a drug or a dietary supplement.
2. Assume for question 1 that the company promoted the product with the claim that it "restores healthy blood" instead. Explain whether this would change your answer to question 1.

Questions 3 through 7 relate to the following hypothetical situation:

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

3. Based on the facts in this case, is Acuxen most likely a food, drug, or dietary supplement, and why? (To answer this question you must consider both the composition of Acuxen and the indication.)
4. If Sue made the root product as a topical patch, why might your answer be different than the previous one?
5. Assuming that the product in question 3 is a dietary supplement based on composition and it is a structure/function claim, on what legal basis could the FDA still challenge the product?
6. Explain why your answer in question 3 might change if Sue labeled Acuxen for use in insomnia? Assuming this is a health or disease claim, would it matter whether the claim was made on the label or in pamphlets attached to the product?
7. Assume that, before purchasing Acuxen, a patient in a pharmacy asked the pharmacist about the product and that the pharmacist remarked that in his opinion the product seemed to be effective for insomnia and also in preventing some types of dementia. Has the pharmacist violated the FDCA?
8. The Exachol decision was issued prior to DSHEA. How might the decision be different today?
9. Differentiate between the disclaimer required for a structure/function claim on a dietary supplement product label and a health claim pursuant to the Pearson decision.

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 section of this chapter.) Section 303 also singles out several violations that warrant much more severe penalties, such as violations of the Prescription Drug Marketing Act discussed in Chapter 3.

Explanation of the Law

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

Product Recalls

One method of removing adulterated or misbranded products in interstate commerce is by means of recall. Prior to the passage of the FDAAA in 2007 the FDA did not have the statutory authority to order a product recall, but rather had to request a company to recall a product as an alternative to injunctive action or seizure. Now the FDA can order a recall, or alternately, a manufacturer may initiate a product recall without FDA involvement. In either event, 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. Many pharmacy publications also provide current lists of recalled products.

ADULTERATION

Adulteration: The Law

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

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

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

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

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

Explanation of Adulteration

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

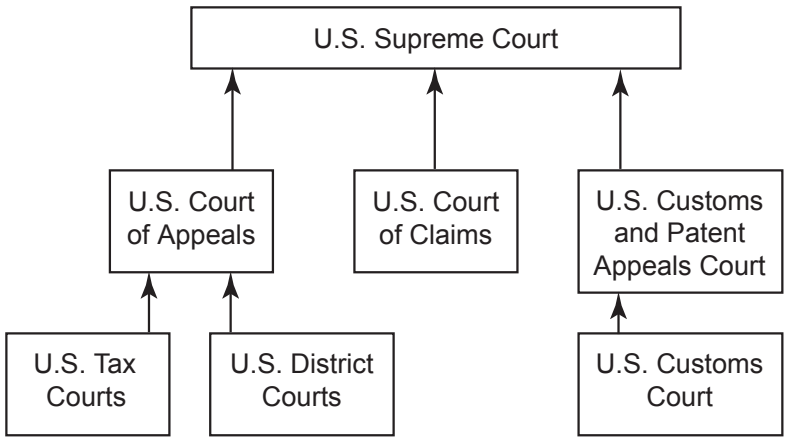

FIGURE 2-1 Federal court system.

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

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

These provisions in the law are intended to regulate the facility and the means of production rather than the product itself.

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

Current Good Manufacturing Practice (CGMP)

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

Product Tampering

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

MISBRANDING

MISBRANDING: THE LAW

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

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

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

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

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

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

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

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

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

(m) If it is a color additive the intended use of which is for the purpose of coloring only, unless its packaging and labeling are in conformity with applicable packaging and labeling requirements.

(n) Unless the manufacturer, packer or distributor includes in all advertisements and other descriptive printed matter a true statement of (1) the established name printed prominently and in type at least half as large as that used for any trade or brand name, (2) the formula showing quantitatively each ingredient of the drug and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness.

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

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

EXPLANATION OF MISBRANDING

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

STUDY SCENARIOS AND QUESTIONS

1. A pharmacist received a bottle of cephalosporin capsules. Unknown to the pharmacist, the tablets also contained small amounts of penicillin. The pharmacist dispensed the capsules to a patient who is allergic to penicillin and who then suffered an anaphylactic shock. Explain whether the drug is misbranded and/or adulterated. Explain whether the pharmacist has violated the FDCA, and if so, whether the pharmacist might face sanction by the FDA.
2. A hospital pharmacy received ampules of a commonly stocked drug contained in a pink solution. The drug has always been in a clear solution previously. The pharmacist dispensed the drug for IV administration. The drug was contaminated and injured the patient. Explain the difference between this situation and the one in question 1 as related to the pharmacist involved.
3. A pharmacist received a prescription for a brand name drug and legally substituted a generic drug. The pharmacist labeled the dispensed generic drug with the brand name drug. Explain whether the pharmacist has violated the FDCA.
4. A pharmacist received a call from a physician who ordered ibuprofen 600 mg for a patient, but instructed the pharmacist to label the drug as oxycodone. Explain whether the pharmacist would violate the FDCA if he or she complies, and whether this situation differs from question 3.
5. A patient hands a pharmacist a prescription for Spondicin 20 mg, a prescription-only drug. As the patient is waiting for the prescription to be filled, the patient notices that Spondicin 10 mg is available over the counter and asks the pharmacist how it can be that one strength is prescription only and the other is OTC. What should the pharmacist say? Would the pharmacist violate the FDCA by telling the patient to use the OTC drug for the prescribed indication in the prescribed dose when that indication or dosage is not contained in the OTC drug's labeling?
6. A pharmaceutical manufacturer issued a Class I recall for one of its prescription drug products. How might a pharmacist learn of this recall? Explain whether a pharmacist would violate the FDCA if he or she dispensed the drug after the recall notice. If it is a violation, explain whether it would be a defense if the pharmacist did not know of the recall.

NEW DRUG APPROVAL

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

(NDA), an extremely expensive and lengthy process.

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

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

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

Defining "New Drug"

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

DRUG ADVERTISING AND PROMOTION

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

The federal government has chosen to regulate the advertising and promotional activities of drug products more strictly than typical products.

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.

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.

PRESCRIPTION DRUG ADVERTISING: MANUFACTURER TO PROFESSIONALS

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

APPLICABLE STATUTE AND REGULATIONS

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

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

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

STUDY SCENARIO

You are the only pharmacist at a meeting with other health care professionals. A physician brings up the topic of direct-to-consumer drug ads on television and in magazines, lamenting that the ads are so seductive and misleading that some of his patients practically demand he prescribe the drugs for them. The physician and the other attendees wonder if the FDA regulates these ads. Explain to the group in attendance the requirements for drug advertising for broadcast and print media.

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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 would also have no difficulty establishing that the product is misbranded because the product's label would not be in compliance with drug labeling requirements.

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

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

The court first described the facts of the case:

> Plaintiffs manufacture and market a product known as "starch blockers" which "block" the human body's digestion of starch as an aid in controlling weight. On July 1, 1982, the Food and Drug Administration ("FDA") classified starch blockers as "drugs" and requested that all such products be removed from the market until FDA approval was received. The next day plaintiffs filed two separate complaints in the district court seeking declaratory judgments that these products are foods under 21 U.S.C. 321(f) and not drugs under 21 U.S.C. 321(g). On October 5, 1982, the district court held that starch blockers were drugs under 21 U.S.C. 321(g), plaintiffs were permanently enjoined from manufacturing and distributing the products, and they were ordered to destroy existing inventories. The portion of the order requiring destruction of the products was stayed pending appeal.
>
> The only issue on appeal is whether starch blockers are foods or drugs under the Federal Food, Drug, and Cosmetic Act. Starch blocker tablets and capsules consist of a protein which is extracted from a certain type of raw kidney bean. That particular protein functions as an alpha-amylase inhibitor; alpha-amylase is an enzyme produced by the body which is utilized in digesting starch. When starch blockers are ingested during a meal, the protein acts to prevent the alpha-amylase enzyme from acting, thus allowing the undigested starch to pass through the body and avoiding the calories that would be realized from its digestion.
>
> Kidney beans, from which alpha-amylase inhibitor is derived, are dangerous if eaten raw. By August 1982, FDA had received 75 reports of adverse effects on people who had taken starch blockers, including complaints of gastrointestinal distress such as bloating, nausea, abdominal pain, constipation, and vomiting. Because plaintiffs consider starch blockers to be food, no testing as required to obtain FDA approval as a new drug has taken place. If starch blockers were drugs, the manufacturers would be required to file a new drug application pursuant to 21 U.S.C. 355 and remove the product from the marketplace until approved as a drug by the FDA.

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

> 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 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 common sensefoods.
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)*

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

Overview

Like the Nutrilab case, this is a case in which a product becomes a drug on the basis of

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

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

The court related the facts of the case:

> Carter-Glogau, located in Glendale, Arizona, was a manufacturer of generic injectable drugs. Carter was the corporation's president and chief operating officer. OJF, located in Maryland Heights, Missouri, was a distributor of prescription pharmaceutical products, primarily generic drugs. Hiland was OJF's president and Madison was its executive vice-president of operations. Almost all of the injectable drugs distributed by OJF were manufactured by Carter-Glogau. In most cases, the drugs manufactured by Carter-Glogau for OJF were generic copies of innovator drugs that were formulated by other companies and approved by the FDA.
>
> In April 1982, one of Carter-Glogau's customers wrote Carter to ask whether an intravenous form of vitamin E could be developed, noting that "[t]here must be a Hell of a market out there." Carter expressed a reluctance to develop such a product. In his responses to the customer's inquiry, he stated that the amount of polysorbates needed "may be detrimental," and pointed out that "fat emulsions for IV use . . . are very tricky products and fraught with particular size problems."

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

> In August 1982, Madison wrote Carter to see if he could develop for OJF a high potency intravenous form of vitamin E for use in premature infants. He informed Carter that Hoffmann-LaRoche, a large pharmaceutical company, was testing an injectable vitamin E product for the treatment of RLF in an effort to obtain FDA approval of the product. Madison wrote that he was "afraid that when Roche gets their vitamin E approved, we will lose the business, unless you can come up with something." Madison's letter clearly indicated that the primary purpose of the product he was proposing would be to treat RLF, and stated, "We could always label it for vitamin E supplementation." Hiland received a copy of this letter.
>
> In his responses to Madison's inquiries, Carter expressed serious safety concerns regarding the development of an intravenous vitamin E product, stating in part: "If we make some attempt to solubilize the vitamin E and use the wrong proportions and kill a few infants, we'd have some serious problems."

> Carter was specifically concerned about developing such a product without proper clinical testing. He wrote Madison that: "The administration of this product intravenously in neonatals without appropriate clinical work concerning toxicity will undoubtedly lead to an exposure in terms of product liability which neither you nor we may wish to assume."

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

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

Decision of the court: The court affirmed the lower court's ruling against the defendants.

Notes on *United States v. Hiland*

1. The FDCA imposes a strict liability (misdemeanor) requirement on product sellers, meaning that the mere introduction into interstate commerce of an unapproved or misbranded drug violates the law, regardless of whether the seller had any knowledge to this effect. The defendants tried to argue that intent to mislead or defraud (a criminal charge) cannot be established unless the government can prove they had knowledge that the product was an unapproved new drug and was misbranded. Usually in a fraud case, the prosecution must show knowledge. The government, however, argued that because knowledge to this effect is not required for the misdemeanor violation, it cannot be required for the fraud violation. The only elements required, argued the government, are that the defendants unknowingly committed the acts and had an intent to defraud. The court dodged the issue of whether knowledge must be proven or not by holding that the facts clearly showed that the defendants knew their product was promoted as a drug and was mislabeled.
2. The defendants contended that they thought they could market their product without approval on the basis of FDA policy. During the DESI review, the FDA had allowed generic drug manufacturers to continue marketing their products pending a determination of efficacy. This policy was voided, however, by a federal court. Even had the policy been valid, it would not have applied to E-Ferol because it only applied to generics whose parent drug had been proven safe and effective. E-Ferol had no parent drug.
3. It is conceivable that if this case was brought today, the defendants would argue that the product is a dietary supplement, not a drug. This argument would not likely prevail, however. First, E-Ferol is intended for injection, and DSHEA defines a dietary supplement as one intended for ingestion. Second, the defendants clearly intended that the IV E-Ferol be used to treat RLF, a disease.