

Chapter 13

Health Professionals and the Regulated Industry: The Laws and Regulations Enforced by the U.S. Food and Drug Administration

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Historical Perspective
General Considerations for Regulated Products
Drugs for Human Use
Biologics
Foods
Cosmetics

Animal Products
Medical Devices
Reporting Problems: Adverse Events and Product Quality Issues
FDA's Role in the "Practice of Medicine"

No textbook in legal medicine would be complete without a discussion of the regulation of health care products for the U.S. marketplace and the role of the U.S. Food and Drug Administration (FDA). The U.S. market is almost unique. Unlike foreign markets, the range of products available to the consumer and the practicing health professional is based on marketability and competitiveness rather than on preselection by a national governmental body. With the advent of managed care, this marketplace is changing. Although many federal agencies have an impact on the regulation of products sold in the United States (Fig. 13-1), the FDA is the main agency responsible for foods, drugs, biologics, medical devices (including energy-emitting products such as cathode ray tubes and microwave ovens), and cosmetics. Approximately one out of every four dollars spent in the United States is under the FDA's jurisdiction. Although foods represent the largest category of consumer purchases, the FDA spends almost twice as much in the regulation of drugs and biologics. This chapter provides an overview of the current laws and regulations governing the manufacture, packaging, import and export, and approval of products for the U.S. marketplace. Also discussed are the requirements for the development of new products and the responsibilities of clinical investigators, manufacturers, and health professionals in the use of both investigational and approved products, as well as for products for which approval is not required.

HISTORICAL PERSPECTIVE

Most food and drug regulation is an outgrowth of consumer concern with the safety of products. Table 13-1 provides a

brief overview of the major legislation affecting U.S. food and drug regulation. Federal legislation dates back to the Drug Importation Act of 1848 requiring U.S. Customs inspection to bar entry of foreign adulterated drugs. It was not until the twentieth century, however, that federal regulatory authority became fully established. Regulation of the purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans was initiated by the 1902 Biologics Control Act. Growing concerns over the unsanitary conditions in meat-packing plants, the use of poisonous preservatives and dyes in foods, and exaggerated claims for unproven and dangerous patent medicines sparked debate over the regulation of foods and drugs. On June 30, 1906, both the first comprehensive Food and Drugs Act and the Meat Inspection Act were signed into law. The new law prohibited the interstate commerce of misbranded and adulterated foods, drinks, and drugs; required disclosure of drug ingredients on the label; and introduced new controls over the manufacturing and processing of foods.

The Food and Drug Administration was formally established as an agency in 1930. By this time many had tried and failed to revise the now outdated 1906 statute. It would take a major disaster—the death of 107 people, mostly children, after ingestion of an “elixir of sulfanilamide” containing a poisonous solvent (ethylene glycol)—to reform the act resulting in the passage of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 United States Code [U.S.C.] 321 to 394). Enacted in 1938, the FDCA continues to be the cornerstone for food and drug regulations in the United States. The FDCA encompassed new and important provisions, the most monumental of which was the requirement that new drugs

124 Health Professionals and the Regulated Industry

<p>Food and Drug Administration (FDA)</p> <ul style="list-style-type: none"> • Foods, drugs, biologics, cosmetics, medical devices, radiation producing devices • Labeling of regulated products • Advertising and promotion of Rx drugs 	<p>Federal Trade Commission (FTC)</p> <ul style="list-style-type: none"> • Advertising and promotion of foods, devices, OTC drugs • Advertising of practices, procedures
<p>Environmental Protection Agency (EPA)</p> <ul style="list-style-type: none"> • Pesticide tolerances 	<p>U.S. Food and Wildlife Service</p> <ul style="list-style-type: none"> • Biodiversity; sustainability
<p>U.S. Department of Agriculture (USDA)</p> <ul style="list-style-type: none"> • Commodities, animal vaccines 	<p>Customs</p> <ul style="list-style-type: none"> • Imports and alerts
<p>Drug Enforcement Administration (DEA)</p> <ul style="list-style-type: none"> • Scheduled substances 	<p>Alcohol, Tobacco and Firearms (ATF)</p> <ul style="list-style-type: none"> • Alcohol and tobacco
	<p>U.S. Postal Service</p> <ul style="list-style-type: none"> • Products shipped or promoted through the U.S. mail

Fig. 13-1. U.S. agencies involved in the regulation of foods and drugs.

1848	Drug Importation Act requires U.S. Customs Service inspection to stop entry of adulterated drugs from overseas.
1902	Biologics Control Act (Virus, Serum, and Toxins Act) ensures purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.
1906	Food and Drugs Act prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs. Meat Inspection Act is passed by Congress on the same day, June 30. Both signed by President Theodore Roosevelt.
1911	Supreme Court rules in <i>U.S. v. Johnson</i> that the 1906 Food and Drugs Act does not prohibit false therapeutic claims—only false and misleading statements about the ingredients or identity of a drug.
1912	Sherley Amendment addresses <i>U.S. v. Johnson</i> rule by prohibiting the labeling of medicines with false therapeutic claims intended to defraud the purchaser, a standard difficult to prove.
1927	Food, Drug, and Insecticide Administration established.
1930	Agency renamed as Food and Drug Administration (FDA) .
1933	Introduction of first Senate bill to launch a five-year legislative battle to update the obsolete Food and Drugs Act 1906 .
1937	Elixir of Sulfanilamide , containing the poisonous solvent diethylene glycol, kills 107 persons, many of whom are children, dramatizing the need to establish drug safety before marketing and to enact the pending food and drug law.
1938	Federal Food, Drug, and Cosmetic (FDC) Act contains new provisions: extends control to cosmetics and therapeutic devices; requires new drugs to be shown safe before marketing, starting a new system of drug regulation; eliminates the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases; provides safe tolerances to be set for unavoidable poisonous substances; authorizes factory inspections; adds the remedy of court injunctions to the previous penalties of seizures and prosecutions. Wheeler-Lea Act charges the Federal Trade Commission with overseeing advertising of FDA-regulated products, except prescription drugs.
1941	Insulin Amendment requires FDA to test and certify purity and potency of this life-saving drug for diabetes.
1943	U.S. v. Dotterweich : Supreme Court rules that responsible officials of a corporation, as well as the corporation itself, may be prosecuted for violations. It need not be proven that the officials intended, or even knew of, the violations.
1944	Public Health Service Act covers a broad spectrum of health concerns, including regulation of biological products and control of communicable diseases.
1945	Penicillin Amendment requires FDA testing and certification of safety and effectiveness of all penicillin products. Later amendments extended this requirement to all antibiotics. Repealed in 1983.
1951	Durham-Humphrey Amendment defines the kinds of drugs that cannot be safely used without medical supervision and restricts their sale to prescription by a licensed practitioner.
1958	Food Additives Amendment requires manufacturers of new food additives to establish safety. The Delaney proviso prohibits the approval of any food additive shown to induce cancer in humans or animals. FDA publishes in the Federal Register the first list of nearly 200 substances, those substances Generally Recognized As Safe (GRAS) .

Table 13-1 Food and drug regulation: key U.S. legislation

1960	Color Additive Amendment enacted, requiring manufacturers to establish the safety of color additives in foods, drugs, and cosmetics. The Delaney proviso prohibits the approval of any color additive shown to induce cancer in humans or animals.
1962	Kefauver-Harris Drug Amendments ensure drug efficacy and greater drug safety following thalidomide disaster. Drug manufacturers now required to prove to FDA the effectiveness of therapeutic products prior to sale. Exempts from the Delaney proviso animal drugs and animal feed additives shown to induce cancer but which leave no detectable levels of residue in the human food supply.
1966	FDA contracts with the National Academy of Sciences/National Research Council to evaluate the effectiveness of 4000 drugs approved on the basis of safety alone between 1938 and 1962.
1968	FDA placed in the Public Health Service. FDA forms the Drug Efficacy Study Implementation (DESI) to implement recommendations of the National Academy of Sciences investigation of effectiveness of drugs first marketed between 1938 and 1962. Radiation Control for Health and Safety Act protects consumers against unnecessary exposure to radiation from electronic products.
1970	Upjohn v. Finch : Court of Appeals upholds enforcement of the 1962 drug effectiveness amendments by ruling that commercial success alone does not constitute substantial evidence of drug safety and efficacy.
1972	Over-the-counter drug review starts to enhance the safety, effectiveness, and appropriate labeling of drugs sold without prescription. Regulation of biologics , including serums, vaccines, and blood products, is transferred from NIH to FDA.
1976	Medical Device Amendments ensure safety and effectiveness of medical devices, including diagnostic products. Manufacturers required to register with FDA and follow quality control procedures. Some products must have premarket approval by FDA; others must meet performance standards before marketing. Vitamins and Minerals Amendments ("Proxmire Amendments") stop FDA from establishing standards limiting potency of vitamins and minerals in food supplements or regulating them as drugs based solely on potency.
1980	Infant Formula Act establishes special FDA controls to ensure necessary nutritional content and safety.
1982	Tamper-Resistant Packaging Regulations issued by FDA to prevent poisonings such as deaths from cyanide placed in Tylenol capsules.
1983	Orphan Drug Act allows FDA to promote research and marketing of drugs needed for treating rare diseases, which have little commercial value. Federal Anti Tampering Act makes it a crime to tamper with packaged consumer products.
1984	Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman) expedites marketing of generic drugs, while providing that brand-name companies can apply for up to 5 years additional patent protection for the new medicines, to make up for time lost while their products were going through FDA's approval process.
1986	National Childhood Vaccine Injury Act requires patient information on vaccines, gives FDA authority to recall biologics, and authorizes civil penalties.
1988	Food and Drug Administration Act officially establishes FDA as an agency of the Department of Health and Human Services with a Commissioner of Food and Drugs appointed by the President with the advice and consent of the Senate, and broadly spells out the responsibilities of the Secretary and the Commissioner for research, enforcement, education, and information. Prescription Drug Marketing Act bans the diversion of prescription drugs from legitimate commercial channels; requires drug wholesalers to be licensed by the states; restricts reimportation from other countries; and bans sale, trade, or purchase of drug samples, and traffic or counterfeiting of redeemable drug coupons.
1990	Nutrition Labeling and Education Act requires all packaged foods to bear nutrition labeling and all health claims for foods to be consistent with terms defined by the Secretary of Health and Human Services. Safe Medical Devices Act authorizes FDA to order device product recalls; requires facilities to report incidents where a medical device may have caused or contributed to a serious adverse event; requires manufacturers to conduct postmarket surveillance on permanently implanted devices whose failure might cause serious harm or death, and to establish methods for tracing and locating patients depending on such devices.
1991	Regulations published to Accelerate the review of drugs for life-threatening diseases.
1992	Generic Drug Enforcement Act imposes debarment and other penalties for illegal acts involving abbreviated drug applications. Prescription Drug User Fee Act requires drug and biologics manufacturers to pay fees for product applications and supplements, and other services. The act also requires FDA to use these funds to hire more reviewers to assess applications.
1994	Dietary Supplement Health and Education Act establishes specific labeling requirements, provides a regulatory framework, and authorizes FDA to promulgate good manufacturing practice regulations for dietary supplements. This act defines "dietary supplements" and "dietary ingredients" and classifies them as food. The act also establishes a commission to recommend how to regulate claims.

Table 13-1 Food and drug regulation: key U.S. legislation—cont'd

126 Health Professionals and the Regulated Industry

1997	<p>Food and Drug Administration Modernization Act reauthorizes the Prescription Drug User Fee Act of 1992 and mandates the most wide-ranging reforms in agency practices since 1938. Provisions include measures to accelerate review of devices, regulate advertising of unapproved uses of approved drugs and devices, and regulate health claims for foods.</p>
1998	<p>FDA promulgates the Pediatric Rule, a regulation that requires manufacturers of selected new and extant drug and biological products to conduct studies to assess their safety and efficacy in children.</p> <p>Mammography Quality Standards Reauthorization Act continues 1992 Act until 2002.</p> <p>First phase to consolidate FDA laboratories nationwide from 19 facilities to 9 by 2014 includes dedication of the first of five new regional laboratories.</p>
1999	<p>ClinicalTrials.gov is founded to provide the public with updated information on enrollment in federally and privately supported clinical research, thereby expanding patient access to studies of promising therapies.</p> <p>A final rule mandates that all over-the-counter drug labels must contain data in a standardized format. These drug facts are designed to provide the patient with easy-to-find information, analogous to the nutrition facts label for foods.</p>
2000	<p>The U.S. Supreme Court, upholding an earlier decision in <i>Food and Drug Administration v. Brown & Williamson Tobacco Corp. et al.</i>, ruled 5–4 that FDA does not have authority to regulate tobacco as a drug. Within weeks of this ruling, FDA revokes its final rule, issued in 1996, which restricted the sale and distribution of cigarettes and smokeless tobacco products to children and adolescents, and which determined that cigarettes and smokeless tobacco products are combination products consisting of a drug (nicotine) and device components intended to deliver nicotine to the body.</p> <p>Federal agencies are required to issue guidelines to maximize the quality, objectivity, utility, and integrity of the information they generate, and to provide a mechanism whereby those affected can secure correction of information that does not meet these guidelines, under the Data Quality Act.</p> <p>Publication of a rule on dietary supplements defines the type of statement that can be labeled regarding the effect of supplements on the structure or function of the body.</p>
2002	<p>The Best Pharmaceuticals for Children Act improves safety and efficacy of patented and off-patent medicines for children. It continues the exclusivity provisions for pediatric drugs as mandated under the Food and Drug Administration Modernization Act of 1997, in which market exclusivity of a drug is extended by six months, and in exchange the manufacturer carries out studies of the effects of drugs when taken by children. The provisions both clarify aspects of the exclusivity period and amend procedures for generic drug approval in cases when pediatric guidelines are added to the labeling.</p> <p>In the wake of the events of September 11, 2001, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 is designed to improve the country's ability to prevent and respond to public health emergencies, and provisions include a requirement that FDA issue regulations to enhance controls over the imported and domestically produced commodities it regulates.</p> <p>Under the Medical Device User Fee and Modernization Act, fees are assessed for sponsors of medical device applications for evaluation, provisions are established for device establishment inspections by accredited third parties, and new requirements emerge for reprocessed single-use devices.</p> <p>The Office of Combination Products is formed within the Office of the Commissioner, as mandated under the Medical Device User Fee and Modernization Act, to oversee review of products that fall into multiple jurisdictions within FDA.</p> <p>An effort to enhance and update the regulation of manufacturing processes and end-product quality of animal and human drugs and biological medicines is announced, the current good manufacturing practice (cGMP) initiative. The goals of the initiative are to focus on the greatest risks to public health in manufacturing procedures, to ensure that process and product quality standards do not impede innovation, and to apply a consistent approach to these issues across FDA.</p>
2003	<p>The Medicare Prescription Drug Improvement and Modernization Act requires, among other elements, that a study be made of how current and emerging technologies can be utilized to make essential information about prescription drugs available to the blind and visually impaired.</p> <p>To help consumers choose heart-healthy foods, the Department of Health and Human Services announces that FDA will require food labels to include trans fat content, the first substantive change to the nutrition facts panel on foods since the label was changed in 1993.</p> <p>An obesity working group is established by the Commissioner of Food and Drugs, charged to develop an action plan to deal with the nation's obesity epidemic from the perspective of FDA. In March 2004 the group releases "Calories Count: Report of the Obesity Working Group," which addresses issues connected to the food label, obesity therapeutics, research needs, the role of education, and other topics.</p>

Table 13-1 Food and drug regulation: key U.S. legislation—cont'd

	<p>The National Academy of Sciences releases “Scientific Criteria to Ensure Safe Food,” a report commissioned by FDA and the Department of Agriculture, which buttresses the value of the Hazard Analysis and Critical Control Point (HACCP) approach to food safety already in place at FDA and invokes the need for continued efforts to make food safety a vital part of our overall public health mission.</p> <p>The Animal Drug User Fee Act permits FDA to collect subsidies for the review of certain animal drug applications from sponsors, analogous to laws passed for the evaluation of other products that FDA regulates, ensuring the safety and effectiveness of drugs for animals and the safety of animals used as foodstuffs.</p> <p>FDA is given clear authority under the Pediatric Research Equity Act to require that sponsors conduct clinical research into pediatric applications for new drugs and biological products.</p>
2004	<p>Project BioShield Act of 2004 authorizes FDA to expedite its review procedures to enable rapid distribution of treatments as countermeasures to chemical, biological, and nuclear agents that may be used in a terrorist attack against the U.S., among other provisions.</p> <p>Passage of the Food Allergy Labeling and Consumer Protection Act requires the labeling of any food that contains a protein derived from any one of the following foods that, as a group, account for the vast majority of food allergies: peanuts, soybeans, cow’s milk, eggs, fish, crustacean shellfish, tree nuts, and wheat.</p> <p>A ban on over-the-counter steroid precursors, increased penalties for making, selling, or possessing illegal steroid precursors, and funds for preventive education to children are features of the Anabolic Steroid Control Act of 2004.</p> <p>FDA publishes “Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products,” which examines the critical path needed to bring therapeutic products to fruition, and how FDA can collaborate in the process, from laboratory to production to end use, to make medical breakthroughs available to those in need as quickly as possible.</p> <p>Based on recent results from controlled clinical studies indicating that Cox-2 selective agents may be connected to an elevated risk of serious cardiovascular events, including heart attack and stroke, FDA issues a public health advisory urging health professionals to limit the use of these drugs.</p> <p>To provide for the treatment of animal species other than cattle, horses, swine, chickens, turkeys, dogs, and cats, as well as other species that may be added at a later time, the Minor Use and Minor Species Animal Health Act is passed to encourage the development of treatments for species that would otherwise attract little interest in the development of veterinary therapies.</p> <p>Deeming such products to present an unreasonable risk of harm, FDA bans dietary supplements containing ephedrine alkaloids based on an increasing number of adverse events linked to these products and the known pharmacology of these alkaloids.</p>
2005	<p>Formation of the Drug Safety Board is announced, consisting of FDA staff and representatives from the National Institutes of Health and the Veterans Administration. The Board will advise the Director, Center for Drug Evaluation and Research, FDA, on drug safety issues and work with the agency in communicating safety information to health professionals and patients.</p>

Adapted from *FDA Backgrounder* BG99-4. Updated November 2006.

Table 13-1 Food and drug regulation: key U.S. legislation—cont’d

be shown to be safe before marketing, marking a new direction in drug regulation. In the ensuing years, the FDA was given expanded responsibilities. In 1951, what became known as the Durham-Humphrey Act established criteria for distinguishing prescription and over-the-counter (OTC) drugs.

Following the thalidomide disaster in the early 1960s, in which pregnant women took a sleep-inducing drug approved in Europe and subsequently gave birth to infants with the severe birth defect, phocomelia, the U.S. Congress passed significant amendments to the FDCA, called the Kefauver-Harris Act. This new legislation now required that drugs not only be proven safe before marketing, but also effective for the intended use.

Over the last 30 years, Congress has continued to expand the FDA’s regulatory responsibilities, necessitating frequent reorganization. The 1966 Fair Packaging and Labeling Act (15 U.S.C. Sections 1451 to 1461) required that all consumer

products in interstate commerce be honestly and informatively labeled, bearing a legible, prominent statement of net quantity of contents in terms of weight, measure, or numerical count. The 1968 Radiation Control for Health and Safety Act expanded the federal government’s regulatory role, protecting consumers against unnecessary exposure to radiation from electronic products, and in 1971 the Bureau of Radiological Health was transferred from the old Nuclear Regulatory Commission to the FDA. In 1972, sections of the Public Health Service (PHS) Act of 1944, addressing biologics for human use (42 U.S.C. 262 to 263), mammography (42 U.S.C. 263b), and control of communicable diseases (42 U.S.C. 264), were also brought under the FDA’s purview.

The mission of the FDA is to enforce laws enacted by the U.S. Congress and to establish and enforce regulations to protect the health, safety, and pocketbook of the consumer.¹ In general, the FDCA is intended to assure the consumer that foods are pure and wholesome, safe to eat, and produced

128 Health Professionals and the Regulated Industry

under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging are truthful, informative, and not deceptive. Today the FDA is organized into five major regulatory centers: the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, the Center for Food Safety and Applied Nutrition, and the Center for Veterinary Medicine.

GENERAL CONSIDERATIONS FOR REGULATED PRODUCTS Premarket Testing and Approval

Prior to marketing, new drugs, biological drugs, and certain devices (including their labeling) must be approved for safety and effectiveness. Substances added to food must be approved as safe, “generally recognized as safe,” or “prior sanctioned.” Premarketing clearances are based on scientific data provided by manufacturers, subject to review and acceptance by government scientists for scope and adequacy. The type and extent of premarket testing required for a particular product depends on how it is categorized and what kinds of claims are made about the product by those with a vested interest in it. Testing may include physical and chemical studies, nonclinical laboratory studies, animal tests, and clinical trials on humans.

Current “Good Practices” [cGxP] Regulations

The importance of the laboratory, animal toxicological, and clinical data derived from premarketing testing demands that these studies be conducted according to sound scientific protocols and procedures. For products under the FDA’s jurisdiction, regulations describing the requirements needed for manufacturing and developing are delineated. The requirements include: Good Laboratory Practices (GLP); Good Manufacturing Practices (GMP); and Good Clinical Practices (GCP). Together the requirements are abbreviated, current GxP. These regulations are codified in Title 21, Code of Federal Regulations. **Good Laboratory Practices** (GLPs) (21 CFR Part 58) address nonclinical laboratory research. For each product category the FDA has published a set of current **Good Manufacturing Practices** (GMPs). GMPs emphasize written records documenting compliance within process controls for every step of the production process. In order to meet GMPs, manufacturing procedures must be validated. Validation documents that the manufacturing processes, the systems, and other procedures will consistently and reproducibly produce the product to prescribed specifications and attributes. GMPs also stipulate adequate training of personnel, maintenance requirements for buildings, facilities, equipment, reliable and secure computerized operations, as well as the avoidance of errors to ensure sanitation. The GMP requirements

for drugs and biologics are far more rigorous than those for foods. Within the foods categories, different types of foods may have different GMP requirements.

Manufacturers, clinical investigators, and clinical trial monitors are expected to know their responsibilities for the clinical evaluation of products. These responsibilities, called current **Good Clinical Practices**, can be found in the regulations, “General Responsibilities of Investigators” (21 CFR Sections 312, Subpart D, and 812, Subparts E and G). GCPs address selection and qualifications of the clinical investigators and the documentation of the commitment of the investigator to supervise and to assume responsibility for those involved in the clinical studies. The cGCP requirements stipulate that a scientifically sound clinical protocol must be followed, control be maintained over the disposition of all test articles, appropriate human subject protection assurances are in place, and the monitoring and reporting of clinical and adverse events (see below).

Enforcement Actions Against Clinical Investigators

Two enforcement tools—*debarment* and *disqualification*—are used by the FDA to protect the integrity of the product approval process. Sponsors or investigators convicted of criminal actions or who are found to have engaged in activities to undermine the drug approval process can be prevented from obtaining or participating in subsequent drug approvals or from providing any services to a drug product applicant. This procedure is called *debarment* and extends to persons working for applicants of human, animal, and biological drug products. Submission of false data to secure approval is a criminal violation of the laws that prohibit giving false information to the government. The FDA is authorized to conduct debarment procedures under the Generic Drug Enforcement Act of 1992 (FDCA Sections 306 to 308), which includes fines ranging up to a million dollars. Clinical investigators conducting studies of investigational drugs, biologics, or devices and who violate FDA regulations can be *disqualified* through informal hearings conducted by the FDA (21 CFR Part 16). Disqualification prevents the investigator from receiving investigational products. Product sponsors must certify that they have not used the services of a disqualified individual or debarred individual or firm in any capacity in connection with a marketing application. The FDA publishes the names of investigators and corporations that have been disqualified, disbarred, or who have signed consent agreements, along with information about their reinstatement.^{2,3}

Adulteration and Misbranding

The FDCA prohibits the import, sale, or distribution of adulterated or misbranded products in the United States. *Adulterated* products are those that are defective, unsafe, filthy, or produced under unsanitary conditions (Sections 402, 501, 601, codified at 21 U.S.C. 342, 351, 361). A product is *misbranded* if it includes statements, designs, or pictures in labeling that are false or misleading, as well as the

failure of the manufacturer to provide required information in labeling (Sections 403, 502, 602, codified at 21 U.S.C. 343, 352, 362). Products required to undergo premarketing approval by the FDA cannot be distributed without such approval, as described above (see Section 704 [21 U.S.C. 374]). Definitions of these terms are included in the law itself and have been interpreted by hundreds of court decisions.

Product Recall and Reporting Systems

Under the FDCA, the FDA has the authority to remove violative products from the market. Removal or the *recall* of products is one of the main means by which the FDA fulfills its mandate of consumer protection. Products failing to meet GMPs or labeling requirements, or those that are defective, are candidates for recall. Voluntary recall is the quickest way for product removal from the market and may be initiated by the manufacturer or shipper of the product, or at the request of the FDA. Recall actions undertaken by industry are reported weekly in the FDA Enforcement Report. Product recalls fall into three categories. Class I designation signifies an imminent health hazard, for which the consequences may be serious illness or death (e.g., incorrect dose, contamination with a pathogenic organism). For a Class I recall, the FDA may order the recall, or the notification to product users, or both. Class II recalls are designated when a product may cause temporary or reversible adverse health consequences, or where the probability of serious consequences is remote (e.g., potency assay does not meet specifications). A Class III recall is designated when it is unlikely that the product will produce adverse health consequences. Class III recalls are often administrative in nature (e.g., label printing errors) and may have little or no impact on the product's use. For medical device recalls, manufacturers are required to notify health professionals by issuing a Medical Device Notification at the FDA's request and to report to the FDA actions undertaken to remove or correct violative devices in commerce. Voluntary Safety Alerts can also be issued.

Although cooperation in a recall may make court proceedings unnecessary to remove the product from the market, it does not relieve a person or firm from possible civil or criminal liability for violations. The FDA prefers, when possible, to promote compliance by other means than going to court. The FDA has the authority to observe conditions or practices of a manufacturer, and during inspections when conditions are noted that may result in violations, a written report (FDA Form 483) of the observations is left with management. By correcting these conditions or practices promptly, manufacturers may bring their operations into compliance. FDA inspectors will also report any voluntary corrective action they witness during an inspection, or that management may bring to their attention. Copies of these reports are available to the public through the FDA's Freedom of Information office.

Product Seizures

The FDA's authority includes the right to seize products. Seizure is a civil court action against goods to remove them

from the channels of commerce. After seizure, the goods may not be altered, used, or moved, except by permission of the court. The owner or claimant of the seized merchandise is usually given about 30 days by the court to decide on a course of action. The claimant may do nothing, in which case the goods will be disposed of by the court; decide to contest the government's charges by filing a claim and answering the charges, and the case will be scheduled for trial; or consent to condemnation of the goods, while requesting permission of the court to bring the goods into compliance with the law. To bring the goods into compliance, the owner of the goods is required to provide a bond (money deposit) to assure the court that the orders will be carried out and must pay for FDA supervision of any compliance procedure.

Federal Anti Tampering Act

The Federal Anti Tampering Act (Pub. L. 98-127), signed into law in 1983, amends Title 18 of the U.S. Code to establish graduated penalties for tampering with intent to cause injury or death. The penalties range from a maximum of \$25,000 and 10 years imprisonment in the case of an attempt to tamper to a maximum of \$100,000 and life imprisonment in a case where death results from the tampering. The law also establishes penalties for tampering with or mislabeling consumer products with intent to injure a business; for knowingly communicating false information that a consumer product has been tainted and if such tainting had occurred, would create a risk of death or bodily injury; and for threatening and conspiracy to tamper with a consumer product. *Consumer product* is defined as including any articles subject to the FDCA, and the FDA is designated as having authority to investigate violations.

Drug and Device Listing and Establishment Registration

Under Section 510 of the FDCA (21 U.S.C. 360; also see 21 CFR 207), listing is required for all drugs, biologics (including blood products), device products, veterinary drugs, and medicated premixed animal feeds. The authority to require registration and listing of blood banks is from the PHS Act (see 21 CFR 607.20-607.21). The FDA uses the National Drug Code numbering system in assigning a number. Registration of establishments is also required. "Establishments" include facilities to manufacture, process, repackage, or otherwise change the container, wrapper, or labeling of a product, and the law applies to both bulk and finished dosage forms, as well as products for export. Failure to register and list is a violation of the law at Section 301(p). Devices for human use proposed for commercial distribution must undergo not only registration, but also premarket notification (Section 510(k), codified at 21 U.S.C. 360(k)) of the FDA at least 90 days before beginning such distribution (21 CFR 807), unless specifically exempted by regulation (Section 514, codified at 21 U.S.C. 360d). This allows the FDA to determine if premarket approval is necessary.

Orphan Products: Regulation and Promotion of Products for Rare Diseases and Conditions

To encourage the development of products for rare conditions and diseases that would not ordinarily be commercially viable for a company, Congress passed the Orphan Drug Act (Pub. L. 97-414, 96 Stat. 2049) in 1983, which amended the FDCA to provide manufacturers with economic incentives. In order to meet the definition of an “orphan product,” the condition must affect fewer than 200,000 persons in the United States annually, or more than 200,000 persons in the United States and for which there is no reasonable expectation that the development cost will be recovered in the domestic sales of the product. On application by the sponsor, such products may qualify for an “Orphan Drug Designation.” Orphan designation of a product does not in any way alter the standard regulatory requirements for marketing approval. However, it does permit tax credits (26 U.S.C. 44H) for clinical research undertaken by a sponsor to generate required data and the granting of exclusive approval for 7 years for a designated drug or biological product. More recently the FDA has also included regulations for devices, called Humanitarian Use Devices (HUDs), for use in conditions affecting less than 4000 persons annually in the U.S. (see 21 CFR 814 Subpart H).⁴

DRUGS FOR HUMAN USE

The United States regulates products by their intended use. *Intended use* is derived from the explicit and implicit claims made in the product’s labeling, and in the product’s advertisements or promotional activities. The FDCA defines drugs

as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals” (FDCA Section 201(g), codified at 21 U.S.C. 321(g)). Thus, even products that are not being currently sold as drugs, including conventional foods, dietary supplements, and cosmetics, are subject to the drug requirements of the law, if therapeutic or prevention claims are made, as illustrated in Fig. 13-2.

Official Drugs

The FDCA recognizes as official drugs those products identified in the following official compendia: the United States Pharmacopeia (USP), the Homeopathic Pharmacopeia of the United States (HPUS), and the National Formulary (NF) (see FDCA Section 201(j)). USP monographs provide standards, specifications, and methods of analysis for approximately 3200 drugs, and the NF monographs contain standards for an additional 250 pharmaceutical materials. All drugs named in the compendia are required by the FDCA to meet the standards of strength, quality, or purity set forth in such compendia and must be packaged and labeled in the manner prescribed by the official compendia. If a drug differs from or falls outside the limits specified in an official compendium, the nature and extent of its difference from such standard must be plainly stated on the label (Section 501(b), codified at 21 U.S.C. 351(b)).⁵

A drug not recognized in an official compendium is adulterated if its strength differs from or its purity or quality falls below that which it purports to have or is represented to possess (Section 501(c), codified at 21 U.S.C. 351(c)).

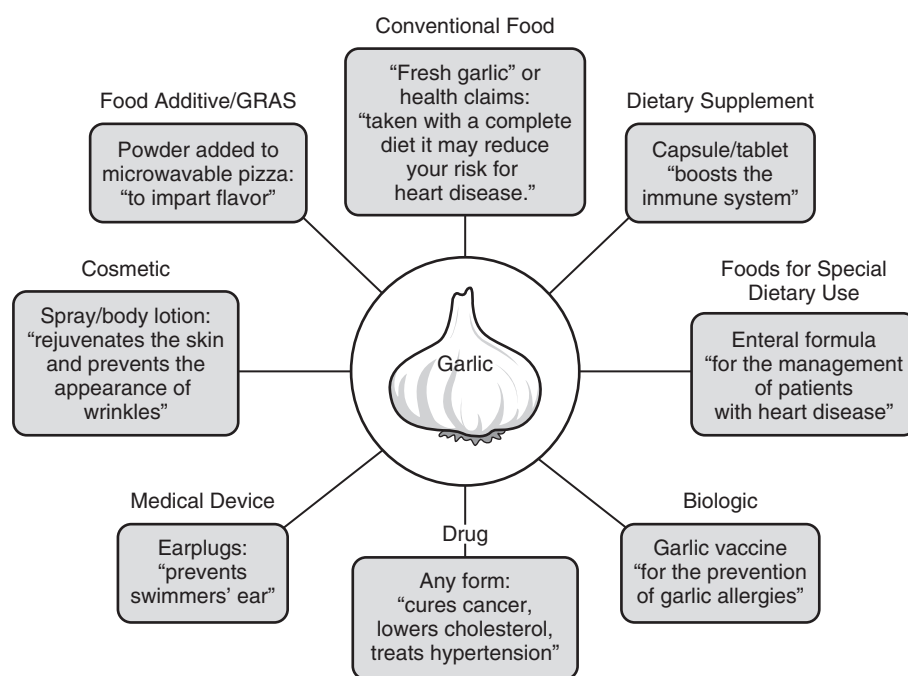


Fig. 13-2. The U.S. Regulatory Classification (e.g., claims for garlic products). (Courtesy Freddie Ann Hoffman, MD, and Thomas Garvey IV, JD.)

For example, any drug intended for use by injection and any ophthalmic ointment or solution must be sterile; if such a product is contaminated with microorganisms, it is adulterated. Also, a drug is adulterated under the FDCA if any substance has been mixed with it so as to reduce the quality or strength of the product or to constitute a substitute of the product (Section 501(d), codified at 21 U.S.C. 351(d)).

Prescription and Nonprescription (Over-the-Counter) Drugs

Up until the Prescription Drug Act of 1951 (also called "Durham-Humphrey"), drugs were generally available to the public. The 1951 amendments required that those drugs that cannot be used safely without professional supervision be dispensed only by prescription because they are habit-forming, toxic, or have too great a potential for harmful effects, or are for medical conditions that cannot be readily self-diagnosed. In addition, if a product cannot be self-administered by the consumer (e.g., intravenous), or if a product cannot be labeled with instructions for use that are reasonably understood by a consumer, it must be dispensed by prescription. Prescription drugs may be dispensed only by or on the prescription of a licensed health practitioner and must bear the statement: "Rx Only" (Section 503(b)(4), added in 1951 by Pub. L. 65-648, codified at 21 U.S.C. 353(b)(4)). The definition of a *licensed practitioner* is a matter of state law and varies from state to state.

A drug is to be made available without a prescription if, by following the labeling, consumers can use it safely and effectively without professional guidance. Nonprescription or "over-the-counter" (OTC) drugs sold directly to consumers are indicated for conditions that are self-limiting and can also be recognized and treated successfully by consumers without professional monitoring. Standards for safety, effectiveness, and labeling for OTC products are described in 21 CFR 330.10(a)(4). With the passage of the Kefauver-Harris Amendments in 1962, documentation of not only a drug's safety but also its efficacy was required for the drug to continue to be marketed in the United States. FDA responded to the mandate by initiating the Drug Efficacy Study Implementation (DESI) program, which reviewed the evidence for safety and efficacy of drugs marketed for the first time between 1938 and 1962. Drugs, such as digitalis, morphine, and phenobarbital, marketed prior to the 1938 FDCA were exempt from review. In 1966, the FDA commissioned expert panels to determine whether sufficient information supported the criterion of "substantial evidence" of effectiveness, as required by the new law. DESI evaluated over 3000 separate products and over 16,000 therapeutic claims. As an outgrowth of the DESI review, the process of the Abbreviated New Drug Application (ANDA) was established. ANDAs were accepted for reviewed products that required changes in existing labeling to be in compliance. In September 1981 final regulatory action had been taken on 90% of all DESI products. By 1984, final action had been completed on 3443 products; of these, 2225 were found to be effective, 1051 were found not effective, and 167 were pending.

The Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984 was a compromise between the brand-name and generic drug industries. The brand-name industry received patent term restoration equal to half the time spent in clinical trials plus all the time that the FDA spent reviewing the New Drug Application. The restoration was limited to a maximum of 5 years and the length of a patent after restoration to 14 years. Innovators also received 5 years of nonpatent exclusivity for a new chemical entity and 3 years of exclusivity for a new indication or dosage form. Generic manufacturers were relieved from the requirement of reproving the safety and efficacy of the active ingredient, but required to show with a degree of statistical precision that their products delivered the same active ingredient to the bloodstream or site of action to the same extent and at the same rate as the innovator products. The current issue of FDA's "List of Approved Drug Products with Therapeutic Equivalence Evaluations" has details and can be downloaded from the FDA website.

In May 1972, the FDA applied the principle of a retrospective review to OTC drugs. The structure for this OTC review needed to be different from that of the prescription drug review, mainly because of the more than 300,000 available OTC products. FDA developed an OTC drug monograph process. At the time the FDA identified more than 80 therapeutic classes and about a thousand active ingredients. For each therapeutic class, ingredients were classified as: Category I, Generally Recognized As Safe and Effective ("GRAS" and "GRAE"); Category II, not GRAS/E; or Category III, insufficient data available to permit classification. The OTC drug monograph is a three-phase rule-making process. It begins with an Advance Notice of Proposed Rule-making (ANPR) based on advisory panel recommendations, followed by a Proposed Rule (PR) (tentative final monograph). A Final Rule (final monograph) taking into account all available information and data for each therapeutic class of drugs is then published in the CFR. To organize its workload, the FDA originally allowed only those ingredients marketed in the United States for a *material time and extent* to be eligible for the monograph process. On January 23, 2002, however, the FDA expanded the monograph process to include ingredients with foreign marketing experience. For each therapeutic drug class (e.g., expectorants, internal analgesics) the OTC monograph delineates acceptable ingredients, dose ranges, formulations, routes, schedules, ingredient combinations, and labeling claims that may appear on OTC drug products. Nonconforming OTC drug products must undergo the new drug review process, as described below.

New Drugs

The 1962 amendments to the FDCA defined a "new" drug as any article marketed after 1938 intended to diagnose, treat, prevent, mitigate, or cure a disease or condition that is not generally recognized as safe or effective (GRAS/E) under the conditions prescribed, recommended, or suggested in the labeling (Section 201(p), codified at 21 U.S.C. 321(p)). Thus, a new drug would require premarket approval by the FDA for safety and efficacy. The FDA reviewed the marketing

132 Health Professionals and the Regulated Industry

applications, called a New Drug Application (NDA) (21 CFR 314) submitted by the drug's sponsor (usually, but not always, its manufacturer), containing acceptable scientific data from tests to evaluate its safety, and *substantial evidence* of effectiveness for the conditions for which the drug is to be offered (Section 505, codified at 21 U.S.C. 355). *Substantial evidence* is defined as "evidence consisting of *adequate and well-controlled investigations*, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" (Section 505(d)). After the FDA approves a drug, the drug's formula, manufacturing process, labeling, packaging, dosage, and methods of testing generally may not be altered or modified from those stated in the NDA, without the approval of a supplemental application (21 CFR 314.70). Although drugs that are not "new" drugs are exempt from the new drug premarketing procedure, they must comply with all other drug requirements, including registration, labeling, and manufacturing practices.

Most prescription drugs are new drugs. In some cases, prescription drugs may be "switched" from prescription to OTC status ("Rx to OTC switch") through a supplemental NDA. To justify the sale of the product directly to the consumer, the information submitted in the application must support the dose, route, indication, and safety of the drug

for nonprescription use. To augment the FDA's resources and to reduce the time to approval of new drugs, in 1992 Congress passed the Prescription Drug User Fee Act (PDUFA; Pub. L. 102-571, Title I). This law authorizes the FDA to collect "user fees" for the filing and review of certain applications for approval of human drug and biological products, and for establishments where the products are made. User fees are not applicable to generic or monographed drugs, whole blood and blood components used for transfusion, some large volume parenterals, allergenic extract products, in vitro diagnostic biological products, and certain drugs derived from bovine blood. Under some specific conditions, the FDA may waive, reduce, or delay payment of the fees.

Investigational Drugs

In order to market a new drug, the sponsor must demonstrate the drug's clinical safety and efficacy for the intended indication. The development of a new drug usually proceeds in an orderly fashion from discovery, through preclinical studies (in vitro and animal studies), clinical studies, to the filing of the NDA (Fig. 13-3). During this process the new drug is considered to be an *investigational new drug* (Section 505(i), codified at 21 U.S.C. 355(i)). An Investigational New Drug (IND) application must be filed with the FDA before an investigational new drug may be distributed across state lines or imported for human trials (21 CFR 50 and 312). A product under an IND may not be promoted or advertised for the indications being studied prior to approval under an

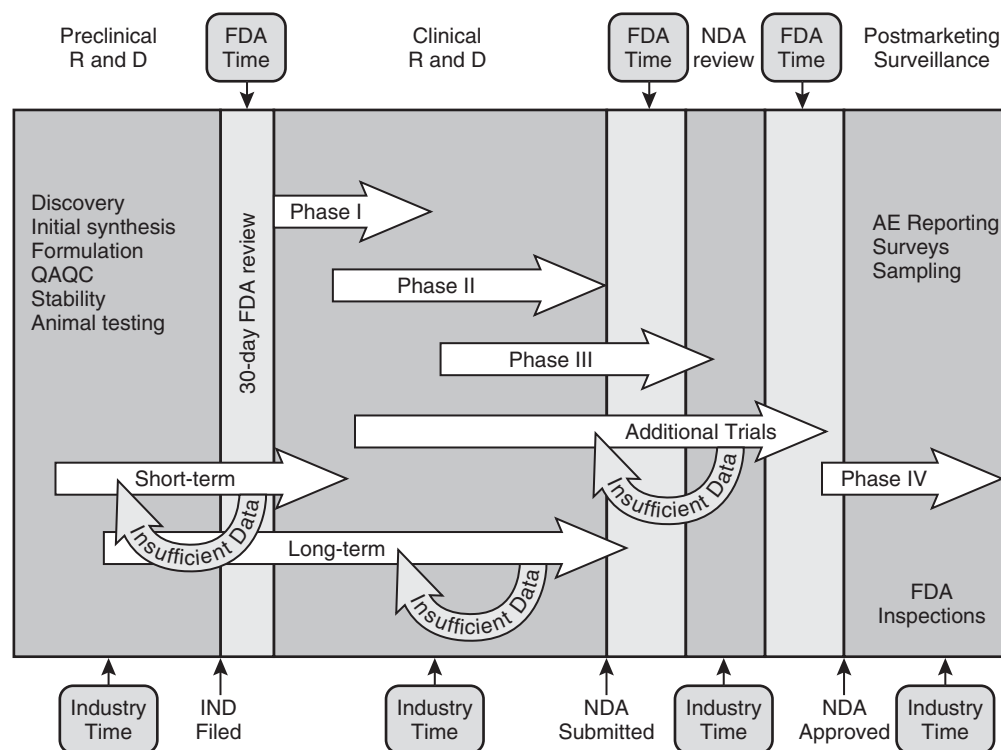


Fig. 13-3. New drug development in the United States.

NDA (21 CFR 312). The clinical evaluation is usually conducted in stages or *phases*. Phase I studies are the initial studies in humans; safety is the main study objective. Phase II studies address safety and efficacy and pharmacokinetics and pharmacodynamics. Although not described in regulation, Phase III trials are large, well-controlled studies. Often these are pivotal studies to confirm the results for submission in the NDA. Postmarketing, or Phase IV studies, may be required by the FDA to elucidate the safety of the product in broader populations or may be carried out by the sponsor to establish a new indication or promotional claim.

The design of the clinical protocol should be supported by information already known about the product. This includes information about the pharmacology, toxicity, and effects observed in preclinical studies, as well as any previous human use that supports the safety of the dose, route, and schedule. Protocols must contain essential elements, which include objectives, a description of the study population, subject selection criteria, product information, monitoring plan, end point determination, and analyses to be performed. The protocol must also be accompanied by an informed consent form that meets the requirements set out in 21 CFR 50.20 and 50.25. The FDA is continually evaluating the risk to benefit ratio in permitting trials to proceed and in approving drugs for the U.S. market. The FDA publishes *Guidance* documents on the design and conduct of preclinical and clinical drug development, as well as on other parts of the development process.

Accelerated Approvals and Expanded Access to Investigational Products

New drugs, antibiotics, and biologics (discussed later) for the treatment of serious or life-threatening illnesses may be developed under expedited procedures (see Subpart E of the regulations 21 CFR 312.80 to 312.88).^{6,7} When the following four criteria exist, a Treatment IND can be filed permitting use by a wider population of promising agents when the product: (1) is intended to treat serious or immediately life-threatening disease; (2) there is no comparable or satisfactory alternative drug or other therapy; (3) is already under investigation in a controlled (Phase II or III) clinical trial or all clinical trials have been completed; and (4) marketing approval is being actively pursued (21 CFR 312.34).⁸ Treatment INDs have been filed for treatments of the human immunodeficiency virus and other serious conditions.

The Label and "Labeling" of Drugs

The FDCA defines label to mean the written, printed, or graphic matter on the immediate container (Section 201(k), codified at 21 U.S.C. 321(k)) and the outer carton or wrapper of the package. Labeling includes all labels and other written, printed, or graphic matter accompanying the product. The word *accompanying* is interpreted very broadly; therefore labeling may include material that does not physically accompany the product, if it serves to identify the article, tell its uses, give directions, and so on. How a drug is

labeled is determined by its classification, that is, whether it is an investigational drug, a new drug, a prescription-only drug, or an OTC drug. Each of these has special labeling requirements.

The label itself must bear identifying information, such as the dosage strength and the quantity of content, active ingredients, expiration date, name and quantity or proportions of any habit-forming substance with appropriate statements (e.g., "Warning: May be habit forming," as stated in Section 502(d), codified at 21 U.S.C. 352(d)). An important provision states that a drug is misbranded if its labeling is false or misleading in any particular (Section 502(a), codified at 21 U.S.C. 352(a)). Prescription drugs must be labeled "Rx Only." The package insert should contain the following sections: description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, overdosing (where applicable), dosage and administration, and how supplied (21 CFR 201.50 through 201.57). For OTC preparations, the principal display panel must bear similar information, as required under 21 CFR 201.61 to 201.62. Additionally, most OTC drug products are required to have tamper-evident packaging and labeling (21 CFR 211.132). Drugs that are dispensed by a licensed practitioner are exempted from the need to use the labeling required in the manufacturer's package if the dispensed products have the pharmacist's label containing the legally required elements, such as the names and addresses of the prescriber and patient, directions for use, and so on (Section 503(b)(2), codified at 21 U.S.C. 353(b)(2)). In addition to the requirements listed, a drug must not imitate another drug or be offered for sale under the name of another drug (Sections 301(I) and 502(I)(2)).

Advertisements for Prescription Drugs

Whereas advertisements for OTC drugs are regulated by the Federal Trade Commission, advertisements for drugs sold by prescription are regulated by the FDA (Section 502(n), codified at 21 U.S.C. 352(n)).⁹ Until the late 1970s, such advertising was directed exclusively to health professionals, although there is no prohibition on advertisements to consumers. The first prescription drug advertised to consumers was a pneumonia vaccine intended for healthy elderly persons who may not be seeing a health professional regularly. In recent years, direct-to-consumer advertisements for prescription drugs have become increasingly common. The regulations for prescription drug advertisements are specific in the kinds of information that is necessary to be included (21 CFR 202). These regulations apply regardless of whether the advertisement is directed to health professionals or consumers. Dissemination of prescription drug advertisements that are not in compliance with the regulations constitutes misbranding. Advertisements may be submitted to the FDA for comment before publication. A drug can be advertised only for those conditions for which the FDA has approved an NDA or an appropriate supplement. These conditions are listed in the approved package insert. By including the term *Physicians' Desk Reference* (PDR) in the definition of labeling, FDA regulations

134 Health Professionals and the Regulated Industry

(21 CFR Section 202.1) require that, if a manufacturer chooses to list a product in the PDR, the listing must be in the same words as the package insert. Testimonials of users constitute misbranding if they give the impression that a preparation is effective for a condition for which it could not otherwise be promoted.

Statements by Sales Representatives

The objective intent of the persons legally responsible for the labeling of drugs is determined by their expressions or may be shown by the circumstances surrounding distribution of a product. For example, the objective intent may be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. The circumstances may show that the article is misbranded because such persons or their representatives know that the drug is offered for a purpose for which it is neither labeled nor advertised (21 CFR Section 201.128). Health professionals wishing to report questionable promotional activities can call FDA's toll-free hotline (888 INFO-FDA or 888-4630-332).

Homeopathic Drugs

Homeopathy is a system of medicine popularized in the 1700s by Samuel Hahnemann in Germany. Based on a "Law of Similars," it contends that "like treats like." For example, a substance that produces symptoms—such as ipecac, which produces nausea and vomiting at pharmacological concentrations—would be expected to treat these same conditions, when administered in smaller concentrations in a homeopathic preparation. In stark contrast to the science of modern pharmacology, a major tenet of homeopathy is the premise that the more dilute a substance is, the more potent it can be in treating symptoms. Traditionally homeopathic drugs are prepared by taking a starting substance through a prescribed series of dilutions and "succussions" (shakings), also termed "potentization," often ending up with such an infinitesimal amount of starting substance as to contain statistically less than one molecule of active drug substance in the final vial. The 1938 FDCA (Copeland Act, after Royall Copeland, a U.S. Senator and homeopathic physician from New York) specifically allows for homeopathic drugs by the law's recognition of the Homeopathic Pharmacopeia of the United States as an official compendium (see above). Therefore, any product labeled as "homeopathic" must, by definition, be a "drug," including products that might otherwise be regulated as biologics or foods. By policy the FDA has deferred regulation of homeopathic drugs, mostly due to their dilute nature and historical lack of safety concerns. However, the agency has not relinquished its authority to require homeopathic drugs to be reviewed as "new" drugs. Thus, homeopathic drugs do not bear the FDA imprimatur of approval for either safety or efficacy, nor do they undergo any formal FDA review process. They must, however, meet all other drug requirements, including GMP and labeling requirements.

BIOLOGICS

Section 351(a) of the Public Health Service (PHS) Act (42 U.S.C. 262) defines a biologic as "...any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product... applicable to the prevention, treatment, or cure of diseases or injuries of man...." Biologics include such vitally important products as polio and measles vaccines, diphtheria and tetanus toxoids, and skin test substances, as well as whole blood and blood components for transfusion. The newer biotech products, such as monoclonal antibodies, cytokines, growth factors, and genetically engineered products, are also regulated as biologics or jointly as "biologic drugs." In September 2002, the FDA announced that regulation of these biologic drugs would be moved from CDER to CBER and integrated with the review of conventional therapeutic agents. Biologics differ from drugs in their legislative history and regulatory approach. The 1902 Virus, Serum, and Toxins Act was enacted following the deaths of 12 children who received improperly prepared diphtheria antitoxin. The comprehensive PHS Act of 1944 amended and updated the regulations for human biologics. Under the PHS Act biologics can also be legally defined as drugs (therapeutics) or devices (e.g., test kits to release blood products for human use) and are subject to all of the adulteration, misbranding, and registration provisions of the FDCA.

Similar to drugs, the development of biologics also requires the filing of an IND application, which is reviewed by the FDA Center for Biologics Evaluation and Research. Because biologics are often derived from living organisms, including human tissues and viruses, they are by nature potentially dangerous if improperly prepared or tested. The regulation of biologics necessarily stresses the demonstration of potency, sterility, purity, and identity (see 21 CFR Part 610). Manufacturing of biologics differs greatly from most single chemical entity drugs products. Biologics consistency and reproducibility are addressed through lot specifications and the control of lot-to-lot variation through strict manufacturing process controls. In addition, such products must undergo a "general safety" test, which is conducted in animals to determine if there is an unsafe batch (Section 610.11). Close surveillance of biologics production, batch-to-batch testing, and research toward improving the quality of biologics are activities conducted by the FDA Center for Biologics Evaluation and Research (CBER), and the development of standards for these products and proper control procedures are backed by the center's research program. CBER also has jurisdiction over banked human tissue intended for transplantation.¹⁰

Batch Samples and Lot Release Protocols

Similar to NDA approvals for drugs, the PHS Act requires biologics have an approved Biologics Licensing Application (BLA) prior to entering into interstate commerce, or for import or export (21 CFR Parts 600 through 680 and Part 211). Before a licensed biological product is

released for commercial sale or use, specified materials must be submitted to and cleared by CBER. These materials include a sample of the product and detailed records of the product's specifications and batch-to-batch consistency. The FDA supplies standard reference preparations for potency tests of certain licensed products, such as anti-toxins, bacterial and viral vaccines, and skin tests. Manufacturers are required to obtain and use these preparations in their testing of licensed products.

Blood Banks

Interstate shipment of blood and blood components requires the issuance of U.S. product and establishment licenses, in accordance with the PHS Act. A licensed blood bank must comply with appropriate federal standards in preparing and testing the products being shipped. In accordance with FDA regulations (21 CFR 607.20 and 607.21), every blood bank collecting units of blood must register with the FDA within 5 days after commencing operations and must submit a list of blood products prepared. All blood banks must operate in compliance with the FDA's current GMP regulations for blood and blood components (21 CFR 606) and are by law subject to FDA inspection once every 2 years. As with other products, blood and blood components must undergo registration and product listing.

FOODS

Foods are defined as (1) articles used for food or drink for humans or other animals, (2) chewing gum, and (3) articles used for components of any such article (FDCA, Section 201(f), codified at 21 U.S.C. 321(f)). Foods are regulated by the Center for Food Safety and Applied Nutrition and include products classified as conventional foods, food additives, spices, dietary supplements, and foods for special dietary use. Except for cooking wine, and beverages with less than 7% alcohol content which are solely within the jurisdiction of the FDA, beer, wine, liquor, liqueur, and other alcoholic beverages are specifically subject to laws enforced by the Bureau of Alcohol, Tobacco and Firearms (BATF) of the U.S. Treasury Department.

In contrast to the more stringent drug GMPs, food GMPs focus on sanitation. A food is considered adulterated, and therefore illegal, if it contains harmful substances that are either added, or occur naturally, that may render it injurious to health; if it has been prepared, packed, or held under unsanitary conditions; or if any part of it is unfit for consumption (see Section 402(a), codified at 21 U.S.C. 342(a)). Raw agricultural products are illegal if they contain residues of pesticides not authorized by, or in excess of, tolerances established by regulations of the Environmental Protection Agency (Section 402(a)(2)(b) and Section 408).

Labeling

The Nutrition Labeling and Education Act (NLEA) of 1990 (Pub. L. 101-535, 104 Stat. 2353) has led to significant changes in the food labeling regulations. The NLEA addresses

three primary areas: the nutrition label, nutrient content claims, and health claims. The regulations specify the nutrition information that must be on the label and the format in which it is to be presented (Fig. 13-4). The regulations further specify the display of which nutrients are required and their order. In addition to these mandatory nutrients, manufacturers may voluntarily choose to include other information, such as other vitamins and minerals for which Recommended Daily Intakes (RDIs) have been established. In addition to nutrients, the NLEA requires standards to define serving sizes (21 CFR 101.12). Nutrient content claims are those that describe the amount of a nutrient in the food (such as "sodium free" or "low fat") and are defined by FDA regulation (21 CFR 101.13). The food label is shown in Fig. 13-4.

Infant formulas and foods for patient populations (e.g., diabetics) are categorized as foods for special dietary use. In 1980 Congress passed the Infant Formula Act (Pub. L. 94-1190), which establishes nutrient requirements (Section 201(z)) and provides the FDA authority to establish GMPs and requirements for nutrient quantity, nutrient quality control, and record-keeping, and for reporting and recalling infant formulas that pose a potential hazard to health.

Dietary Supplement Health and Education Act of 1994

The Dietary Supplement Health and Education Act (DSHEA) (Pub. L. 103-417, 108 Stat. 4325) of 1994 amended the FDCA to establish a new category of foods. A dietary supplement is a product (other than tobacco) that is intended to supplement the diet. It can be composed of a vitamin, mineral, herb or other botanical, amino acid, dietary substance or concentrate, metabolite, constituent, extract, or combination of these ingredients, and includes drugs and biologics, if marketed as a dietary supplement of food prior to approval. Under DSHEA a dietary supplement is adulterated if it or one of its ingredients presents "a significant or unreasonable risk of illness or injury" when used as directed on the label or under normal conditions of use. A dietary supplement that contains a new dietary ingredient (i.e., an ingredient not marketed for dietary supplement use in the United States before October 15, 1994) must demonstrate that there is adequate information to provide reasonable assurance that the ingredient will not present a significant or unreasonable risk of illness or injury in a New Dietary Ingredient (NDI) notification which is submitted to the FDA at least 75 days prior to marketing the dietary supplement. Unlike the confidential filing of an IND, the NDI notification is in the public domain. The Secretary of the Department of Health and Human Services (DHHS) may also declare that a dietary supplement or dietary ingredient poses an imminent hazard to public health or safety. However, as with any other foods, it is a manufacturer's responsibility to ensure that its products are safe and properly labeled before marketing. The agency is in the process of promulgating regulations for dietary supplements, including GMPs, which will revise 21 CFR 101.36. As part of the provisions of the DSHEA, retail outlets may display educational

136 Health Professionals and the Regulated Industry

The new food label will carry an up-to-date, easier-to-use nutrition information guide, to be required on almost all packaged foods (compared to about 60 percent of products up till now). The guide will serve as a key to help in planning a healthy diet.*

Serving sizes are now more consistent across product lines, are stated in both household and metric measures, and reflect the amounts people actually eat.

The list of nutrients covers those most important to the health of today's consumers, most of whom need to worry about getting too much of certain nutrients (fat, for example), rather than too few vitamins or minerals, as in the past.

The label of larger packages may now tell the number of calories per gram of fat, carbohydrate, and protein.

Nutrition Facts	
Serving Size 1 cup (228g)	
Servings Per Container 2	
Amount Per Serving	
Calories 260 Calories from Fat 120	
% Daily Value*	
Total Fat 13g	20%
Saturated Fat 5g	25%
Cholesterol 30mg	10%
Sodium 660mg	28%
Total Carbohydrate 31g	10%
Dietary Fiber 0g	0%
Sugars 5g	
Protein 5g	
Vitamin A 4%	Vitamin C 2%
Calcium 15%	Iron 4%
* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:	
	Calories: 2,000 2,500
Total Fat	Less than 65g 80g
Sat Fat	Less than 20g 25g
Cholesterol	Less than 300mg 300mg
Sodium	Less than 2,400mg 2,400mg
Total Carbohydrate	300g 375g
Dietary Fiber	25g 30g
Calories per gram:	
Fat 9 • Carbohydrate 4 • Protein 4	

New title signals that the label contains the newly required information.

Calories from fat are now shown on the label to help consumers meet dietary guidelines that recommend people get no more than 30 percent of the calories in their overall diet from fat.

% Daily Value shows how a food fits into the overall daily diet.

Daily Values are also something new. Some are maximums, as with fat (65 grams or less); others are minimums, as with carbohydrate (300 grams or more). The daily values for a 2,000- and 2,500-calorie diet must be listed on the label of larger packages.

* This label is only a sample. Exact specifications are in the final rules. Source: Food and Drug Administration, 1994

Fig. 13-4. The food label at a glance. (From DHHS, FDA, *Focus on Food Labeling: Read the Label, Set a Healthy Table*. An FDA Consumer Special Report. May 1993, DHHS Publication No. 93-2262.)

materials about the health-related benefits of the dietary supplement or its ingredients. These materials, which can include articles, book chapters, scientific abstracts, or other third-party publications, cannot be false or misleading, cannot promote a specific brand of supplement, and must be displayed with other similar materials to present a balanced view. The literature must be displayed separately from the dietary supplements themselves and may not

have other information attached, such as product promotional literature.

Dietary Supplement Claims

Under the new legislation, dietary supplements may make four types of claims: health claims, nutrient content claims, structure or function claims, and claims of well-being.

Health claims must be preapproved by the FDA and describe a relationship between a food substance and a disease or health-related condition (e.g. "Healthful diets with adequate folate may reduce a woman's risk of having a child with a brain or spinal cord birth defect"). Once approved, any food product that meets the criteria to bear the claim may do so without further review or approval by the FDA. Claims of *nutritional support* are statements about classical nutrient deficiency diseases (a product containing sufficient vitamin C to prevent scurvy) and are permissible as long as such statements disclose the prevalence of the disease in the United States. DSHEA also authorizes manufacturers to describe the role of a nutrient or dietary ingredient intended to affect a structure or function in humans (e.g., "calcium builds strong bones," "fiber maintains bowel regularity," "antioxidants maintain cell integrity"), or on general *well-being* ("ginseng makes you feel more energetic"). To support these claims manufacturers must have substantiation that the statements are truthful and not misleading. In addition, the product label must bear the statement: "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." Unlike health claims, nutritional support statements, structure or function claims, and claims of well-being are not subject to FDA preapproval, although the agency must receive notification of the claims no later than 30 days after a product that bears the claim is first marketed. Similar to other foods, dietary supplement products must bear ingredient labeling. If a supplement is covered by specifications in an official compendium and is represented as conforming, it is misbranded if it fails to conform to those specifications. If not covered by a compendium, a dietary supplement must be the product identified on the label and have the strength it is represented as having. Nutrition labeling is also required.

Foods for Special Dietary Uses and Foods Used as Drugs

Foods for special dietary uses (FSDU) are another category under the food section of the law (FDCA Section 411(c)(3), codified at 21 U.S.C. 350(c)(3)). FSDU may supply a special dietary need that exists because of a physical, physiological, pathological, or other condition, including but not limited to the conditions of disease, convalescence, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, or the need to control the intake of sodium. An example might be the foods used in phenylketonuria diets. When a FSDU, or for that matter any food or dietary supplement, is labeled, advertised, or promoted with claims of disease prevention, treatment, mitigation, cure, or diagnosis, the FDA regards these claims as *drug claims*. Such products must comply with the drug provisions of the FDCA, unless the claim is a *health claim* authorized by regulation. Also, if a food ingredient is recognized in an *official compendium*, such as the USP, the product is considered to be both a drug and a food (see later discussion) and may be an ingredient of products that fall into both of these regulatory categories. For example, calcium is an ingredient that is marketed not

only as a dietary supplement, but also is included under the OTC drug monograph as a stomach antacid.

COSMETICS

Cosmetics, like foods, are under the jurisdiction of the FDA Center for Food Safety and Applied Nutrition (CFSAN). U.S.-marketed cosmetics must comply with the FDCA, as well as the Fair Packaging and Labeling Act, and the regulations issued under the authority of these laws (21 CFR Parts 700 to 740). FDCA defines cosmetics as *articles intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions*. Included in this definition are products such as skin creams, lotions, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, shampoos, permanent waves, hair colors, toothpastes, deodorants, and any ingredient intended for use as a component of a cosmetic product. Soap products consisting primarily of an alkali salt of fatty acid and making no label claim other than cleansing of the human body are not considered cosmetics under the law.

With the exception of color additives and a few prohibited ingredients, cosmetic manufacturers may, on their own responsibility, use essentially any raw material as a cosmetic ingredient and market the product without prior FDA approval. Cosmetic manufacturers are not required to test their products for safety; however, the FDA strongly urges cosmetic manufacturers to conduct appropriate safety testing of their products. There is no mandatory registration for cosmetic products. Although firms may voluntarily make available safety data or other information before a product is marketed, voluntary registration and assignment of a registration number by the agency do not confer approval of a firm, raw material, or product by the FDA (21 CFR Parts 710, 720, and 730).

Cosmetic Labeling and Cosmetic Drugs

Cosmetics distributed domestically must comply with labeling regulations under the FDCA and the Fair Packaging and Labeling Act (21 CFR Parts 701 and 740). Some cosmetics must bear label warnings or cautions prescribed by regulation (21 CFR 740). Declaration of ingredients is only required for cosmetics produced or distributed for retail sale to consumers for their personal care (21 CFR 701.3). Some cosmetics are also intended to treat or prevent disease, or affect the structure or function of the human body. Examples include fluoride toothpastes, sun-tanning preparations intended to protect against sunburn, antiperspirants that are also deodorants, and antidandruff shampoos. These products are regulated as cosmetic drugs, and must comply with both drug and cosmetic provisions of the law. Cosmetics that are also drugs must first identify the active drug ingredient(s) before listing the cosmetic ingredients (21 CFR 701.3(d)).

ANIMAL PRODUCTS

The FDA regulates drugs, devices, feeds, pet foods, and the color and food additives intended for animals under

138 Health Professionals and the Regulated Industry

the FDCA. In contrast, animal biologics (e.g., vaccines) are regulated under the Animal Virus, Serum, and Toxins Act (AVSTA) of 1913 (21 U.S.C Sections 151 et seq.), which has been subsequently amended. The AVSTA is under the authority of the Veterinary Biologics Staff of the Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture. Many of the requirements for veterinary products are similar to those for the comparable human products. To protect the national food supply, the FDCA requires the approval of applications for use of new animal drugs in the manufacture of animal feeds. Products administered or used by food-producing animals are evaluated for not only their effect on the animal, but also for their residues in food tissues, such as meat, milk, and eggs. As with human products, a "new animal drug" may not be marketed or imported for commercial marketing unless it has been approved as safe and effective in the United States.

Pesticidal Drugs

Depending on the claims made, animal products that are pesticidal preparations, such as rodenticides, fungicides, and insecticides, may be subject both to the FDCA and the Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C, Sections 136 et seq.), administered by the Pesticide Registration Division of the Environmental Protection Agency. A Memorandum of Understanding between the two agencies specifies which agency will process petitions for products subject to dual jurisdiction. Petitions may be submitted to either agency and will be referred, if necessary.

MEDICAL DEVICES

The FDCA defines a medical device as any health care product that does not achieve its principal intended purposes by chemical action in or on the body or by being metabolized. FDA regulates several thousand medical device products, from simple articles such as tongue depressors and heating pads to in vitro test kits, contraceptive devices, anesthesia machines, and heart valves. In 1968 the Radiation Control for Health and Safety Act was enacted to protect the public from unnecessary exposure to radiation from electronic products (Sections 531 to 542). Thus, electronic products and radiation control are also under the FDA's purview (21 CFR Parts 1000 to 1050). The Medical Device Amendments of 1976 revised and extended the device requirements of the 1938 FDCA, resulting in significant new authority to ensure safe and effective devices. Later the Safe Medical Devices Act (SMDA) of 1990 and the Medical Device Amendments of 1992 enhanced premarket and postmarket controls and provided for additional regulatory authority.

Based on the 1976 amendments, devices fall into three regulatory classes. Class I devices (e.g., tongue blades) are subject to "general controls" that apply to all devices. General controls include the registration of manufacturers, record-keeping requirements, labeling requirements, and

compliance with GMP regulations. Class II devices (e.g., catheters) are subject to "special controls" where general controls are insufficient to ensure safety and effectiveness, and for which enough information exists to develop special controls to provide such assurance, including performance standards, postmarket surveillance, patient registries, guidelines, recommendations, and other appropriate actions. Class III devices include those devices that are life-supporting or life-sustaining (e.g., implants, anesthesia equipment), where special controls are necessary to provide adequate assurance of the safety and efficacy. Similar to new drugs, Class III devices must undergo premarket approval through the filing of an Investigational Device Exemption (IDE) application and a Premarketing Application (PMA). Such devices must have FDA approval for safety and effectiveness before they can be marketed, unless the FDA determines that premarket approval is unnecessary. FDA can require premarket approval of Class I or II devices, if general controls are insufficient to ensure safety and effectiveness and insufficient information is available to establish special controls. Regulations on classification of devices are in 21 CFR 860 and in Parts 862 through 892. All manufacturers are required to give premarket notification (Section 510(k)) giving the FDA 90 days to determine whether or not the device is "substantially equivalent" to a pre-amendment device. For a complete review of the regulations, see 21 CFR Part 860 through 892.

Investigational Devices

Class III and, in some cases, Class II devices may require clinical studies for marketing. While studies are ongoing to determine their safety and effectiveness, the devices are considered *investigational devices* (Section 520(g)). Similar to the drug and biologics regulations, sponsors who wish to conduct these investigations can be granted exemptions from certain requirements of the FDCA, by filing an IDE application 21 CFR 812 (general) and 813 (intraocular lenses). Unlike the drug regulations, if a study is reviewed and found to be of nonsignificant risk to the subjects by an Institutional Review Board, the trial may be conducted without filing an IDE. However, the FDA may later require an IDE to be filed if the manufacturer must submit a Premarketing Application (PMA). Consultation with the agency staff is recommended.

Custom Devices

Custom medical devices ordered by health professionals to conform to their own special needs or to those of their patients (e.g., certain dental devices and specially designed orthopedic footwear) are considered *custom devices* and are exempt from registration and otherwise applicable performance standards or premarket approval requirements (Section 520(b)). The exemption applies only to devices not generally available to or used by other health professionals. Custom devices are not exempt from other provisions of the FDCA and regulations.

REPORTING PROBLEMS: ADVERSE EVENTS AND PRODUCT QUALITY ISSUES

An *adverse drug experience* is defined by the regulations (21 CFR 310.305(b)(2)) as "... any adverse event associated with the use of a drug in humans, whether or not considered drug related." This includes adverse events occurring in the course of the use of a drug product in professional practice; as a result of an overdose, whether accidental or intentional; as a result of abuse or recreational use; from withdrawal; and as any reaction that occurs because of a failure to produce an expected pharmacological or biological action. Adverse effects can range from mild side effects to severe reactions, including death. Adverse experiences that result in death, hospitalization, or permanent disability are always considered serious. Cancer, congenital anomalies, and overdose are adverse drug experiences that are also considered serious. Events may be predictable or unpredictable. Predictable events are most often expected extensions of an individual product's known properties and are responsible for the majority of events encountered. Unpredictable events, however, include idiosyncratic reactions, immunological or allergic reactions, and carcinogenic or teratogenic events. Unlike predictable events, these events are usually not associated with the known pharmacological activity of the product. They seem to be more a function of patient susceptibility than the intrinsic toxicity of the drug. They are rarely avoidable and are generally independent of dose, route, or schedule of administration. Unpredictable events are often among the most serious and potentially life-threatening of all adverse events and are the major cause of important drug-induced disease.

The reporting of adverse events may lead to the discovery of new uses. The phocomelia (limb reduction defects) seen in children whose mothers took thalidomide during the early stages of pregnancy is now thought to be due to inhibition of the formation of new blood vessels. Because of this activity, this same drug is now undergoing clinical trials as an anticancer agent. Excessive hair growth seen in clinical trials of minoxidil tablets (Loniten) for the treatment of hypertension led to development of topical minoxidil (Rogaine) for the treatment of baldness.

Although reporting by health professionals remains voluntary, product sponsors are required to keep the FDA informed regarding any developments that may affect the safety and effectiveness of their products, whether under clinical study or after FDA approval for marketing. (See FDCA, Sections 505(i), (j), and (k), and 21 CFR 310.303, 310.304, 310.305, 312.32, and 314.) Adverse events that occur during clinical studies are to be reported to the FDA, as specified in the regulations for Investigational New Drugs for drugs and biologics or Investigational Device Exemption for devices. For products already marketed, adverse events should be reported to the FDA through MedWATCH. The MedWATCH form (FDA form 3500) allows for the reporting of all FDA-regulated products. In addition, the Vaccine Adverse Event Reporting System

(VAERS) program was established by the National Childhood Vaccine Injury Act of 1986.¹¹ The FDA jointly manages the VAERS program, a joint surveillance program for human vaccine products, with the Centers for Disease Control and Prevention, located in Atlanta, Georgia. The CDC focuses on collective reports, attempting to detect unusual epidemiological trends and associations. The FDA reviews individual reports, assessing whether a reported event is adequately reflected in product labeling, including directions for use. The FDA also closely monitors reporting trends for individual vaccine manufacturers and vaccine lots, which may lead to manufacturing improvements, or in some cases where necessary, the recall of the product from the market. Adverse events can be reported on the FDA website (www.fda.gov), by telephone (1-800-FDA-1088), modem (1-800-FDA-7737), or fax (1-800-FDA-0178). VAERS forms may be obtained by calling 1-800-822-7967.

Drug and Device Quality Reporting System

FDA's Drug Quality Reporting System (DQRS) is a voluntary system to monitor the quality of drugs and devices. Reportable problems include improper labeling, defects, performance failures, poor packaging, and incomplete or confusing instructions. Problems may be reported at the agency's toll-free hotline (888 INFO-FDA or 888-4630-332).

FDA'S ROLE IN THE "PRACTICE OF MEDICINE"

Although the FDA regulates most products used in the practice of the healing arts (e.g., medicine, dentistry, acupuncture), nevertheless, it does not directly regulate the practitioners themselves. Where applicable, the approvals and licensing of health professionals are left to the jurisdiction of the states (see Chapter 2). In addition, the FDA does not regulate procedures, techniques, or lifestyle interventions, such as diet or exercise, or surgical procedures. Procedures such as bone marrow transplantation are considered *technologies* that are evaluated by both federal and private organizations. Such *technology assessments* can have a major impact on whether insurance carriers or health management organizations will allow or reimburse for the procedures.

Unlabeled Uses of FDA-Approved Products

Although the FDCA prohibits a manufacturer or distributor from promoting an approved drug or device or unapproved use for an approved product, the FDCA does not prohibit the manner of use by a health professional in the direct management of patients. Once a product has been approved for marketing, a practitioner may prescribe the drug for *unapproved* or, more accurately, *unlabeled* uses, which may be appropriate under certain circumstances and may in fact reflect approaches that have been extensively

140 Health Professionals and the Regulated Industry

reported in the medical literature.¹² Indeed, valid new uses for marketed products are often first discovered by innovative approaches taken by health professionals, which are later confirmed by well-controlled clinical trials. Before the product's label may be revised to include new indications, the substantiating data must be submitted to the FDA for review and approval. This process takes time, and without the cooperation of the manufacturer whose product is involved, it may never occur. For this reason, accepted medical practice often includes unlabeled uses that are not reflected in the product's current labeling. The FDA has taken a similar stance with respect to medical devices. For veterinary practice, two new laws have amended the FDCA, expanding the ability of veterinarians to prescribe unlabeled uses for animals. The Animal Medicinal Drug Use Clarification Act of 1994 allows veterinarians to prescribe extralabel use of not only veterinary drugs, but also approved human drugs for animals under specific circumstances. The Animal Drug Availability Act of 1996 allows the FDA to modify its current definition of "substantial effectiveness" and supports flexible labeling, by broadening the drug approval process to extrapolate information to "minor" species—those animals that are too few in number to allow cost recovery from the development of indications for these species.

Product Resales and Samples

Section 503 of the FDCA (codified at 21 U.S.C. 353), as amended by the Prescription Drug Marketing Act, prohibits the sale, purchase, or trade of prescription drug samples and drug coupons. A drug sample is a unit of a prescription drug that is not intended to be sold, but is intended to promote the sale of the drug product. A coupon is a form that may be redeemed at no—or reduced—cost for a prescription drug. The law also prohibits resale of prescription drugs purchased by hospitals or other health care entities, or donated or supplied at reduced cost to charitable organizations. Exceptions for group purchasing organizations, non-profit affiliates, and entities under common control are provided in the FDCA. Additional exceptions provide for medical emergencies and for dispensing of drugs pursuant to a prescription. Under Section 503 a manufacturer or distributor is also permitted to distribute drug samples to a licensed practitioner or pharmacy of a health care entity by mail or by other means on written request.

Industry-Supported Continuing Medical Education

Scientific and educational activities on FDA-regulated products directed at health care professionals that are performed by or on behalf of the companies that market the products have traditionally been viewed by the FDA as subject to regulation under the labeling and advertising provisions of the FDCA. On November 27, 1992, the FDA published a draft policy statement (57 F.R. 56412)¹³ to distinguish between those activities supported by companies that are otherwise independent from the promotional influence of the supporting

company and those that are not. On October 8, 1996, the FDA finalized this statement (61 F.R. 52800–52801), identifying 12 factors that the agency will consider in determining whether a manufacturer through its support of scientific and educational activities evidenced a "new use" of its drugs or devices. This statement was further clarified in another FDA statement issued on March 16, 2000 (65 F.R. 14286–14288). The final policy statement was the product of extensive consultation with scientific and health care professionals, regulated industry, consumer groups, and other government agencies. This policy, which speaks to FDA-regulated companies that support continuing medical education (CME), reflects documents issued by the Accreditation Council for Continuing Medical Education speaking to accredited providers, the Association of American Medical Colleges speaking to CME faculty members, and the American Medical Association speaking to physicians. Representatives of these organizations, academia, industry, and CME providers meet regularly as the National Task Force for CME Provider/Industry Collaboration hosted by the American Medical Association.

Alternative or Complementary Medical Practices

Although the FDA has no legal or regulatory definition for complementary or alternative medicine (CAM), it does regulate medical products used in such practices, particularly when claims of diagnostic or therapeutic intent are made. As in the conventional practice of medicine, the FDA does not regulate the use of massage, light or music therapy, meditation, or prayer per se. However, when any product is used and promoted for the purpose of diagnosing, preventing, treating, curing, or mitigating human or animal illness, by definition in the FDCA it becomes a drug or device. The FDA does not comment on the source or historical controversies that may surround a use of a particular product, and many useful and well-accepted approved drugs and devices were derived from unusual and unexpected sources. Since 1992, when Congress appropriated funding to the National Institutes of Health (NIH) to establish an Office of Complementary and Alternative Medicine (now the National Center for Complementary and Alternative Medicine), there has been a marked increase in research conducted into the uses and roles of previously unaccepted interventions. As the result of the increased interest in clinical investigation with such products, the FDA has provided guidances to the industry regarding the evaluation of some product categories. One such guidance is the "Draft Guidance for Industry on the Development of Botanical Drugs" (August 10, 2000). FDA has also responded to the public's concerns to examine not only the uses, but also the potential harmful effects, of CAM products.

Importation of Products for Personal Use

Consumers may receive prescription drugs only through a licensed practitioner or, on his or her order, by a registered pharmacist. Under certain limited circumstances, a limited

supply of drugs may be shipped directly to a consumer, for personal use only from a foreign source, in accordance with the personal importation guidance policy. Importation is generally permitted for those products representing a supply for 3 months or less of therapy and that are personally carried, shipped by a personal noncommercial representative of the consignee, or shipped from a foreign medical facility where a person has undergone treatment. FDA personnel do not routinely inspect mail or personal baggage. U.S. Customs brings items to the FDA's attention and the U.S. Postal Service may also become involved. Generally denied entries are large shipments of which the quantity suggests commercial distribution and small shipments solicited by traditional mail order promotions.¹⁴

Endnotes

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3. DHHS, FDA, 21 CFR Part 812. *Investigational Device Exemptions; Disqualification of Clinical Investigators, final rule*, 62(50) *Federal Register* 12087-12096 (Friday, March 14, 1997).
4. DHHS, FDA, 21 CFR Parts 20 and 814. *Medical Devices; Humanitarian Use Devices, final rule*, 61(124) *Federal Register* 33232-33248 (Wednesday, June 26, 1996).
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14. FDA, Chapter 9-71 *Coverage of Personal Importations*, *FDA Regulatory Procedures Manual*, Part 9, *Import Procedures* (1988).

