Kirk-Othmer Encyclopedia of Chemical Technology.

REGULATORY AGENCIES, PHARMACEUTICALS AND COSMETICS

The U.S. Food and Drug Administration (FDA) is the primary federal scientific and regulatory government agency that monitors drug, biologic, medical devices, food, veterinary, and cosmetic products. It has been estimated that Americans spend approximately 25 cents of every dollar on FDA-regulated products (1). FDA employs approximately 9500 people, of whom chemists are the second most numerous, totaling over 1100 persons. Among the other technical personnel that compose the core of the agency are physicians, pharmacists, pharmacologists, biologists, toxicologists, microbiologists, and statisticians.

FDA's mission has traditionally been consumer protection. However, the manner in which the agency accomplishes its regulatory mission has been changing with the explosion of advances within analytical chemistry and toxicology. Because new and better compounds are continuously being developed, increased attention is being devoted to the dilemma of speeding their entry into the market while ensuring their safety and effectiveness. Scientists must not only develop new compounds, but also explain how the benefits outweigh the risks so that society can benefit from their work. Because no compound is completely safe, FDA must make an assessment of the intended use and determine whether the level of risk is acceptable. Only when FDA is able to make timely, scientifically based judgments on data will society reap the rewards of science. For example, FDA has taken the position that society is willing to accept a higher degree of risk for a life-saving device or drug than for a cosmetic or food additive. Making these judgments in a scientific and political context is the responsibility of FDA.

As a regulatory agency staffed by scientists making decisions on a daily basis, FDA's obligations are significant from both a health and safety and an economic perspective. The quality of the scientific expertise both within the FDA and relied on by the agency plays a key role in each and every FDA decision. Because FDA's regulatory foundation is tied to the basic sciences, it would be unable to perform almost any of its multiple activities without the data and information generated by the basic scientific principles and information contained in this *Encyclopedia* and other publications.

1. History of the FDA

American food and drug law is as old as American colonial tradition. As early as 1630, the Massachusetts Bay Colony fined Nicholas Knopp five pounds for selling a worthless concoction as a scurvy remedy. Between 1879 and 1906, some 190 separate measures affecting food and drugs were introduced in Congress. Although few of these bills passed, it was clear that with the physical and geographical redistribution of consumers and sources of consumables, urban dwellers could not protect themselves from nonobvious product defects. The processing, preserving, and pretreating of foods and the development of better drugs for common ailments led to a declining ability to protect oneself from fraud and injury. However, it was not until the passage of the Pure Food and Drug Act of 1906 that the federal government became the primary force in protecting consumers by regulating the interstate distribution of drugs and food. The 1906 Act was the first comprehensive federal law

that defined and regulated adulterated and misbranded foods and drugs. From the 1906 Act, the FDA received its mission and authority to begin its role as a policing agency.

In 1938, Congress significantly modified and expanded the basic framework of the 1906 Act with the Federal Food, Drug, and Cosmetic Act (the Act). The new law extended the concept of drug regulation by requiring that prior to marketing a new drug, an application had to be submitted which provided evidence that the drug was safe. The 1938 Act, which remains the basis of later law, was enacted largely because of the improper formulation of a sulfanilamide product which caused the deaths of over 100 people. With this new Act, FDA's enforcement powers were significantly enlarged and cosmetics and medical devices came under FDA regulation for the first time (2, 3).

Congress expanded FDA's authority in 1962 with the Drug Amendments of 1962, which stipulated that, before a drug could be marketed, it must be shown to be effective as well as safe. In 1976, Congress similarly expanded FDA's authority over medical devices with the Medical Device Amendments.

Other expansions of FDA's authority include the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the 1984 Amendments or the Waxman-Hatch Act, which was passed to attain quicker marketing of safe, effective, and less expensive generic drugs; and the Safe Medical Device Amendments of 1990, which was passed to correct perceived weaknesses in the implementation of the 1976 Device Amendments. Congress further expanded FDA authority over nutrition labeling and health and nutrient content claims on food labels with the Nutrition Labeling and Education Act of 1990.

2. FDA Organization and Roles

The FDA is headed by the Commissioner of Food and Drugs. This position is not a Cabinet-level office but falls within the Public Health Service (PHS), a division within the U.S. Department of Health and Human Services (HHS). The post of FDA Commissioner is subject to HHS political clearance and Senate confirmation, and the Commissioner is ultimately accountable to HHS, Congress, and the President of the United States. The Commissioner has a staff to assist in policy making and several deputy commissioners to oversee operation of all the subordinate units. FDA has six regional offices within the country, each responsible for a section of the country, and 21 district offices. Persons with technical background typically work in one of FDA's chemistry laboratories or as investigators or consumer safety officers.

The FDA's approval and enforcement programs are administered by five centers organized along product lines. Although all five centers must follow the general provisions of the Act, each center is governed by its own unique and distinctive set of laws and regulations. The five centers are as follow.

(*1*) Center for Drug Evaluation and Research (CDER). This center is responsible for the regulation and approval of all branded and generic human drugs, including prescription, over-the-counter, and antibiotic drugs. A drug is defined by the Act as an article intended either to be used in the diagnosis, cure, prevention, mitigation, or treatment of disease in humans or animals, or to affect the structure or any function of the body (4).

(*2*) Center for Biologics Evaluation and Research (CBER). This center is responsible for the regulation and approval of all biological products intended for use in the treatment, prevention, or cure of diseases or injuries to humans. A biological product is any virus, therapeutic serum, toxin, antitoxin, vaccine, blood or blood component or derivative, or analogous product (5). It also includes products produced by biotechnology, such as interferons and erythropoietins.

(*3*) Center for Devices and Radiological Health (CDRH). This center is responsible for the regulation and approval of medical devices as well as such products as x-ray machines and color television sets. A medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or any related article intended either for use in the diagnosis of conditions or the diagnosis, cure, treatment, mitigation, or prevention of disease, or to affect the structure or any function of the body (6). Medical devices

are distinguished from drugs in that devices do not achieve their primary intended purpose through chemical action in the body and need not be metabolized.

(*4*) Center for Food Safety and Applied Nutrition (CFSAN). This center is responsible for the regulation and approval of food for human consumption, food additives, color additives, and cosmetics. Although CFSAN does not regulate meat and poultry, it does set safety and sanitation standards for supermarkets, restaurants, and other retail food establishments.

(*5*) Center for Veterinary Medicine (CVM). This center is responsible for the regulation and approval of animal food and drug products. The center also ensures that animal drugs and medicated feeds are safe and effective and that food from treated animals is safe to eat.

Independent of these centers, the FDA also has overlapping jurisdiction with several other federal agencies, including the U.S. Department of Agriculture; the Bureau of Alcohol, Tobacco, and Firearms; the Federal Trade Commission; and the Environmental Protection Agency.

Most (∼90%) of the FDA's work involves enforcement of the Act. Its consumer protection function includes premarket approval and quality standards for drugs and medical devices, factory inspections, and market surveillance. FDA can combat transgressions such as the mislabeling of drugs or the adulteration of foods by issuing press releases and/or warning letters, seizing products, recommending criminal prosecutions of violators to the Department of Justice, or seeking injunctions in federal courts against companies that manufacture or ship products which do not meet legal or regulatory standards necessary for consumer safety.

Because each center has its own rules and regulations, the best way to understand FDA's regulatory role is to review FDA's regulation of drug, biologic, medical device, food, veterinary, and cosmetic products separately.

2.1. Regulating Drug Products

The FDA has the authority to regulate new drugs from early laboratory research through clinical testing and market approval. In order to be approved for marketing, a new drug must be shown to be both safe and effective for its intended use (7). Safety means a low incidence of adverse reactions or insignificant side effects under adequate directions for use and warnings; it also means low potential for harm which may result from abuse under stated conditions or widespread availability. Effectiveness means a reasonable expectation that the pharmacological effect of the drug will provide clinically significant relief of the type claimed for that drug in a significant proportion of the target population when used with proper directions and warnings.

The FDA new drug approval process, which is the way most products enter the market, begins with clinical investigations. However, before clinical investigations can commence, FDA requires significant preclinical investigations involving tests on laboratory animals. These tests are to determine the nature of the chemical and to establish evidence concerning the toxicity of the substance. If, through animal studies, the drug is determined to be safe enough for human experimentation, an Investigational New Drug (IND) Application must be submitted to the Center for Drug Evaluation and Research before beginning human clinical trials. No human clinical studies may be started until 30 days after FDA has been notified.

FDA's control of clinical drug investigations is derived from the Act's prohibition of the shipment of an unapproved new drug in interstate commerce. The Act also specifically authorizes FDA to require INDs. Accordingly, FDA has implemented IND regulations that shape and control IND investigations (8). Additionally, regulations regarding the rights of human subjects, informed consent, the sale of investigational drugs, and the obligations of sponsors, monitors, investigators, and Institutional Review Boards (IRBs) have also been adopted to implement the statutory IND language (9).

Clinical investigations are broken into three phases, all of which are conducted under the oversight of an IRB to ensure that appropriate safeguards exist to protect the rights and welfare of the research subjects. The first phase of clinical investigation involves the initial administration of the drug to a small number of healthy human subjects in order to test for toxicity, drug metabolism, absorption, elimination, administration,

safe dosage, and other pharmacological information. The second phase covers trials using a limited number of patients for specific disease control or for assessing diagnostic, prophylactic, or other medical use. Tests in this phase usually consist of several hundred patients and take up to two years. Less than one third of the drugs that begin the IND process typically proceed beyond this stage, usually because of safety concerns. The third phase entails large-scale clinical trials on individuals with the relevant condition. These trials can begin only if the data generated in the first two phases provide reasonable assurance that the drug is safe and effective. The third phase is intended to document safety, effectiveness, optimal dosage schedule, side effects, and directions for use in the treatment or prevention of the disease or condition. FDA typically meets with the drug firm throughout clinical trials in the third phase to identify special problems and additional testing that might be needed.

After all clinical trials are completed, the sponsor of the drug submits a New Drug Application (NDA) to FDA. The NDA consists of the IND data, manufacturing information, and data on drug stability (10). To facilitate timely review, FDA classifies all NDAs according to their therapeutic potential as compared to previously marketed drugs. Type A indicates therapeutic gain; Type B, modest therapeutic gain; Type C, little or no therapeutic gain; and Type D, both therapeutic gain and risks. Drugs proposed for use in AIDS treatments are classified as I-AA for priority review.

In order to be approved, an NDA must include data which demonstrate that the drug is both safe and effective. Each NDA is assigned to a division within CDER for consideration and administrative control, and then assigned to the appropriate therapeutic group within the division for review. The primary team of reviewers typically consists of a physician, a pharmacologist or toxicologist, and a chemist.

Other offices within CDER may become involved in the review process via consults. For example, the Office of Epidemiology and Biostatistics analyzes statistical data, the Office of Research Resources provides bioavailability reviews, and the Office of Compliance determines from the results of inspections whether the firms meet FDA's Current Good Manufacturing Practice (cGMP) regulations. Advisory committees composed of independent experts are often asked to meet and further analyze the data. Often they also advise as to what additional data and information may be needed. After FDA's review is completed, FDA issues either a Summary Basis of Approval (SBA) for the drug or a recommendation against approval. If approved, FDA releases the SBA and a summary of the safety and effectiveness data to the general public.

Regulating drug quality is a federal concern that is reflected beyond the approval process. FDA has implemented extensive regulations to ensure that drug products that are produced and marketed, as well as their chemical constituents, continue to meet high standards of quality, purity, and safety, and have the identity and strength accurately represented.

The most far-reaching program for ensuring the quality of marketed drug products is the system of cGMP regulations (11). The cGMP requirements are enforced at two stages of the development and marketing of pharmaceuticals. FDA will refuse to approve an NDA if it determines that the proposed methods, facilities, and controls are inadequate to preserve the identity, strength, quality, and purity of the drug. Once a new drug is approved, the cGMP requirements are enforced through a system of FDA inspections of manufacturing establishments.

Several classifications exist within the broad category of pharmaceuticals, each of which has its own definition and form of regulation. For example, there is a special regulatory category for drugs that are intended to treat rare diseases or conditions, ie, orphan drug products. Because the development of these drugs cannot be economically viable without some form of government assistance, Congress has passed legislation to provide incentives for drug manufacturers to develop these drugs. These incentives include a period of marketing exclusivity for approved drugs that obtain orphan status, as well as U.S. tax credits and possible direct government financial assistance.

Another distinct class of drugs are those requiring a prescription or a written order from a physician or health professional. Congress authorized FDA to determine whether a drug should be a prescription drug. Typically prescription drugs are those that (*1*) have habit-forming characteristics; (*2*) require a physician's

supervision, because of toxic or other harmful effects, methods of use, or collateral measures necessary for use; or (*3*) are limited to prescription use under an NDA.

Drugs which are available without a prescription are readily available to consumers over-the-counter (OTC) (12). An OTC drug is low in toxicity, has low potential for harm, can be labeled for safe use without a doctor's supervision, is not habit-forming, and can be taken under easily understood conditions. The Act distinguishes between new drugs and those that are generally recognized as safe and effective. Because many OTC drugs have been marketed for years, FDA has subjected most OTC drugs to a significantly less restrictive set of regulations. This result stems from the statutory and pragmatic view that, given the agency's limited resources and the lesser hazards associated with OTC products which are generally used to alleviate symptoms rather than treat diseases, OTC products require less review. Therefore, most OTC drugs are excluded from new drug status, and no NDA has to be submitted if the active ingredient or combination of active ingredients is found to be safe and effective by the FDA as announced in final OTC drug regulations, and if the labeling of the product conforms to these OTC drug regulations.

Another subcategory of drugs are those that are reviewed under the Abbreviated New Drug Application (ANDA) process (13). These drugs are usually called generic drugs. A generic drug is one that is equivalent to a pioneer or brand-name drug but is not marketed until the brand-name drug's patent and exclusivity periods have expired. Until the 1984 Amendments, all manufacturers trying to market a new drug were required to generate their own data supporting the safety and effectiveness of their versions of the product, even if a drug with an identical active ingredient had already gone through the NDA process. The 1984 Amendments allowed generic drugs to be approved on the basis of abbreviated NDAs (ANDAs). This abbreviated approval process has the dual purpose of getting safe, effective, and less expensive generic drugs on the market, and of extending the term of patent protection to pioneers in recognition of the need for original research by pharmaceutical companies.

Although generic drugs must meet the same standards as new drug products for identity, strength, purity, stability, adequate labeling, and bioequivalence, they need not go through the extensive clinical trials of a NDA. Instead, these generic drugs must show bioequivalence to the pioneer drug and fall into acceptable parameters set for bioavailability, which is the extent and rate at which the body absorbs the drug. By reducing the testing time, the cost of bringing the drug to market can be reduced by millions of dollars.

Finally, a different set of rules is applied to antibiotics and insulin-containing drugs (14). These categories are regulated under a monograph system mandated by statute. Thus, when a drug in these categories has been demonstrated to be safe and effective to the satisfaction of FDA, the agency promulgates a regulation of general applicability, describing in detail the required specifications of the drug. Thereafter, manufacturers meeting the standards in that regulation may obtain FDA clearance for their own product without submission of any data on safety and effectiveness, other than data demonstrating bioequivalence to the original product. Thus, later versions of a monographed antibiotic or insulin drug product are treated in a manner similar to generic drugs. Another historic distinguishing feature of this category of drugs was the requirement of batch certification. Under this requirement, the manufacturer would submit a sample from a batch of its product to FDA for testing to ensure that the batch meets the stated potency value. The batch requirement was eliminated by FDA in 1982.

2.2. Regulating Biological Products

The process for gaining FDA approval for a biological product is similar to that for a drug product. The FDA regulations require that the person or entity, eg, manufacturer, sponsoring or conducting a clinical study for the purpose of investigating a potential biological drug product's safety and effectiveness submit an IND to the Center for Biological Evaluation and Research. Clinical trials are subject to IRB review, just as drug studies. After completing the IND studies, the manufacturer submits the safety and effectiveness data generated by the studies to FDA in the form of a product license application (PLA). It is the responsibility of FDA to review the

proposed labeling, the preclinical (animal and laboratory) data, the clinical (human testing) data, as well as the facilities utilized and the methodologies employed in the manufacture of the product to determine whether the product is safe and effective for its intended use. Biological products are unique in that, in addition to receiving approval of a PLA, the establishment manufacturing the biologic is subject to a prelicense inspection of the facility and the processes used to produce the potential licensed product. If both product and facility meet all standards and regulations, FDA will approve a PLA for the product and an establishment license application (ELA) for the facility (15).

2.3. Regulating Medical Devices

A person or company engaged in the manufacture, preparation, compounding, assembly, or processing of a device intended for human use must follow the regulations enforced by FDA's Center for Devices and Radiological Health. The level of FDA regulation or control is governed by the class in which the device is placed by the agency, ie, Class I, II, or III (16). Class I devices are those requiring the lowest level of regulation and are subject to general control requirements. These general controls include establishment registration; device listing; premarket notification, ie, 510(k), submission; and cGMP requirements. Class II devices are subject to special controls as well as the general control requirements. Special controls may include labeling and mandatory performance standards or other requirements. Class III devices are subject to general controls and cannot be marketed until they have an approved Premarket Approval Application (PMA) or, as a result of premarket notification (510(k)) submission, until they have been found by FDA to be substantially equivalent to preamendment devices.

Unless otherwise exempt, a firm must submit a premarket notification, also called a 510(k), to the FDA 90 days before it intends to market a device for the first time (17). The 510(k) submission must contain sufficient information to show that the device in question is substantially equivalent to a legally marketed device for a particular intended use. This notification is also required for a product when there is a change or modification to a product that may significantly affect the safety or effectiveness of the device, or when there is a significant change or modification to the intended use of the device.

Class III devices, unless they are substantially equivalent to a device already marketed without a PMA application, require formal FDA approval through the PMA process before initial sale. The PMA process is comparable to the new drug approval process (18). In both cases, safety and effectiveness data must be reviewed by FDA prior to marketing. An approved PMA application acts like a private license granted to the applicant to market a particular device. Other firms seeking to market the same type of device for the same use must also have an approved PMA.

PMA requirements differ between preamendment and post-amendment devices. Preamendment devices are those in commercial distribution before May 28, 1976; post-amendment devices are those first commercially distributed after the date. Class III post-amendment devices that are not substantially equivalent to preamendment Class III devices are considered new devices. Manufacturers of such devices are required to obtain PMA application approval before marketing these. If the post-amendment device is substantially equivalent to a preamendment device and FDA has not initiated a regulatory process specifically requiring the submission of a PMA for the device category, a 510(k) submission can be made.

To allow manufacturers to develop clinical safety and effectiveness data on devices requiring a PMA submission, FDA has implemented regulations that exempt devices intended solely for investigational use from certain provisions of the Act. This exemption is known as the Investigational Device Exemption (IDE) and allows manufacturers of devices intended solely for human investigational use to ship these products through interstate commerce (19). Like the IND regulations, the IDE regulations shape and control the investigational research. If a device is not considered to present a significant risk, an IDE submission to FDA is not necessary. If a device is considered to present a significant risk, an IDE application must be submitted to FDA for approval. In both cases, patient informed consent and IRB approval and oversight is required.

Every device manufacturer, regardless of the device class, must adhere to the requirements set forth in the device cGMP regulations (20). The essential objective of the cGMP regulations is to create a quality assurance system so that the finished device meets all the necessary specifications to maintain a high manufacturing standard. The cGMP regulations cover the methods, facilities, and controls used in preproduction design validation, manufacturing, packaging, storing, and installing medical devices. FDA monitors compliance with the cGMP regulations during its inspection of the firm's manufacturing facilities. To address the variety and complexity of devices, the cGMP regulations designate two device categories: noncritical and critical. General requirements apply to all devices, and critical devices must meet additional cGMP requirements.

2.4. Regulating Food Products

The mandate of the Center for Food Safety and Applied Nutrition (CFSAN) includes U.S. food processors, dietary supplement manufacturers, food warehouses, and cosmetic products. U.S. food processors spend $1.4 billion annually on research and development and introduce 10,000 new grocery products each year. CFSAN monitors over 3000 food additives, thousands of pathogens, and hundreds of pesticides. In addition, the Center is responsible for handling issues involving imported food; inspecting interstate food preparations, ie, mail, planes, and boats; securing safety and sanitation standards for supermarkets, restaurants, and other retail food establishments; as well as all food labeling issues. When the 1906 Act was adopted, food adulteration and misrepresentation were rampant. Over the years, the mandate of FDA with respect to food has expanded beyond its initial role of safeguarding food against contaminants, chemical adulteration, and disease to protecting the purchaser from economic fraud, mislabeling, excessive claims, and other nonsafety offenses such as inaccurate nutrition labeling.

FDA regulates not only the finished food product, but also the ingredients that are added to food. These ingredients may be either intentionally added to food or the unintended result of materials leaching to food from product packaging. Ingredients that are intentionally added directly to food fall into two separate categories: (*1*) pre-1958 substances and substances generally recognized as safe (GRAS) by scientific experts, and (*2*) food additives (21). There are two types of food additives, these that are added directly to food and those that are not intentionally added directly to food but come into contact with food. The latter are considered indirect food additives.

An ingredient used in food prior to January 1, 1958 can be considered GRAS under the conditions of its intended use based on common use in food. FDA prior approval generally is not necessary. A post-1958 food ingredient that is generally recognized by qualified experts as safe, under the conditions of its intended use based on scientific tests, is GRAS by definition and therefore is not a food additive and does not require FDA approval prior to use.

Any substance that is not GRAS or sanctioned by use prior to 1958 (prior sanctioned) is considered a food additive. The Act prohibits the marketing of a food additive unless FDA has published a regulation that approves the intended use of the substance (22). A food additive is deemed unsafe if it is used without an approving regulation; a food is deemed adulterated if it is, bears, or contains an unapproved food additive.

To further improve the general safety standards, the Delaney Clause was included in the Food Additives Amendment of 1958. The Delaney Clause states that no food additive or color additive can be deemed safe if it has been found to induce cancer when ingested by humans or animals (23). The Clause acts as an absolute prohibition on the use of any additive found to cause cancer without any regard for whether, or to what extent, the substance is hazardous to human health. As scientific advances continue, both in the realm of food technology and analysis of previously undetected contaminants, the zero-risk standard of the Delaney Clause will no doubt be revisited to ensure that both the goals of safety and innovation are met.

2.5. Regulating Veterinary Products

Prior to 1968, the laws surrounding veterinary products were unclear and confusing. For example, a drug for use in feeding animals, such as a penicillin product intended to help growth and prevent diseases, was classified as both a drug and a food additive because it was added to a food for animal ingestion. The burden of seeking double clearance and preparing double paperwork before being able to market a product led to strong industry support for the New Animal Drug Amendments adopted in 1968.

Animal drug controls are similar to those for human drugs. The sponsor of a new animal drug must demonstrate both safety and effectiveness of the drug for a particular intended use before a New Animal Drug Application (NADA) is approved (24). Manufacturers of generic animal drugs may submit Abbreviated New Animal Drug Applications (ANADAs), which are comparable to abbreviated new drug applications submitted by manufacturers of human generic drugs.

A distinct concern arises in the area of veterinary drugs because of the possibility that drug residues may be conveyed to humans by the food-producing animals. Therefore, drug residues and their safety in human food remain a central issue for the Center for Veterinary Medicine (CVM). Animal drugs also include those products which promotional literature claims to improve feed efficiency and increase milk production. An animal food product is regulated under the 1968 Animal Drug Amendments if it contains a drug used in feed or premixes (25).

The food additive and GRAS rules applicable to human foods generally apply to animal food ingredients. However, the Delaney clause's prohibition against carcinogenic substances in food additives was amended to permit carcinogenic chemicals to be fed to animals if the animals are not adversely affected and no residue can be found after slaughter.

FDA's medical device regulations relating to adulteration and misbranding generally apply to devices intended for use on animals. These devices, however, are exempt from the 510(k) and PMA requirements. FDA has viewed animal grooming products as being outside of its purview.

2.6. Regulating Cosmetics

Cosmetics are among the least regulated of all FDA product categories. The Act defines a cosmetic as an article, or a component of an article, intended to be used on or in the human body for "cleansing, beautifying, promoting attractiveness, or altering the appearance" of the user (26). The FDA has no statutory preapproval authority over cosmetics. FDA's enforcement mechanism against cosmetics stems from the adulteration and misbranding sections of the Act (27). A cosmetic is considered adulterated if it contains a substance which makes it harmful to users under customary conditions of use, if it contains any "filthy, putrid, or decomposed" substance, or if it is prepared under unsanitary conditions in which the product may have become contaminated.

A cosmetic is considered misbranded if the labeling is considered false or misleading. The FDA has also challenged some cosmetics as being unapproved new drugs when the product labeling suggests therapeutic or other drug value to the consumer. For example, FDA considers cosmetic products to be drugs when these products use terms such as active ingredient or claim pharmacological effects. The FDA has stated that drug–cosmetic distinction rests upon the intended use of the product, and that the administration reviews each product on a case-by-case basis. FDA has the burden of proving that a cosmetic is unsafe. This is a significant deterrent to cosmetic regulatory action because FDA must decide the amount of risk that is acceptable.

BIBLIOGRAPHY

"Regulatory Agencies" in *ECT* 3rd ed., Vol. 20, pp. 108–127, by N. R. Passow, C-E Lummus.

Cited Publications

1. W. Schultz, testimony before the Subcommittee on Health and the Environment of the House Committee on Commerce, 104th Congress, 1st session, Washington, D.C., Feb. 2, 1995.
2. Federal Food, Drug, and Cosmetic Act of 1938 (as amended), 21 USC §§321–395 (1995).
3. 21 CFR §§1–1499 (1995).
4. Ref. 2, §321(g)(i).
5. Ref. 3, part 600.
6. Ref. 2, §321(h).
7. Ref. 2, §321(p), 355; Ref. 3, part 310.
8. Ref. 3, part 312.
9. Ref. 3, parts 312.50 and 312.56.
10. Ref. 3, part 314.
11. Ref. 3, parts 210–211.
12. Ref. 3, parts 330–358.
13. Ref. 2, §355(j).
14. Ref. 2, §§356–357; Ref. 3, parts 429–460.
15. Ref. 3, part 601.
16. Ref. 2, §306(c).
17. Ref. 2, §360(k); Ref. 3, parts 807.81–807.100.
18. Ref. 2, §360(e); Ref. 3, part 814.
19. Ref. 3, part 812.
20. Ref. 3, part 820.
21. Ref. 2, §321(s); Ref. 3, part 170.
22. Ref. 2, §348(a).
23. Ref. 2, §348(c)(3).
24. Ref. 2, §§321(w) and 360(b); Ref. 3, parts 510 and 514.
25. Ref. 2, §321(x), 360(b).
26. Ref. 2, §321(i).
27. Ref. 2, §§361–362.

General References

28. D. O. Beers, *Generic and Innovator Drugs: A Guide to FDA Approval Requirements*, th ed., Aspen Law and Business/Aspen, Engelwood Cliffs, N.J., 1995.
29. Food and Drug Law Institute, *Seventy-Fifth Anniversary Commorative Volume of Food and Drug Law*, Food and Drug Law Institute, Washington, D.C., 1984.
30. Food and Drug Administration, Center for Devices and Radiological Health, *An Introduction to Medical Device Regulations*, HHS Publication No. 92-4222, U.S. Department of Health and Human Services, Public Health Service, Rockville, Md., 1992.
31. Food and Drug Administration, History Office, *A Guide to the Resources on the History of the Food and Drug Administration*, GPO, Washington, D.C, 1995.
32. J. E. Foulke, *Cosmetic Ingredients*, HHS Publication No. 93-5013, Department of Health and Human Services, GPO, Washington, D.C., 1993.
33. *Decoding the Cosmetic Label*, HHS Publication No. 95-5016, Department of Health and Human Services, GPO, Washington, D.C., 1995.
34. W. F. Janssen, *The U.S. Food and Drug Law: How It Came, How It Works*, HHS Publication No. 92-1054, Department of Health and Human Services, GPO, Washington, D.C., 1992.

35. J. T. O'Reilly, *Food and Drug Administration*, 2 vols, 2nd ed., Shepard's/McGraw-Hill, Colorado Springs, Colo., 1993.
36. D. Stehlin, *Cosmetic Safety More Complex Than At First Blush*, HHS Publication No. 93-5012, Department of Health and Human Services, GPO, Washington, D.C., 1993.

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