

Milestones of Drug Regulation in the United States

- 1820** Eleven physicians meet in Washington, D.C., to establish the **U.S. Pharmacopeia**, the first compendium of standard drugs for the United States.
- 1848** **Drug Importation Act** passed by Congress requires U.S. Customs Service inspection to stop entry of adulterated drugs from overseas.
- 1883** **Dr. Harvey W. Wiley** becomes chief chemist, expanding the Bureau of Chemistry's food adulteration studies. Campaigning for a federal law, Dr. Wiley is called the "Crusading Chemist" and "Father of the Pure Food and Drugs Act." He retired from government service in 1912 and died in 1930.
- 1902** The **Biologics Control Act** is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.
- 1905** Samuel Hopkins Adams' ten-part expose of the patent medicine industry, "**The Great American Fraud**," begins in Collier's.
- The American Medical Association, through its Council on Pharmacy and Chemistry, initiates a **voluntary program of drug approval** that would last until 1955. To earn the right to advertise in AMA and related journals, companies submitted evidence, for review by the Council and outside experts, to support their therapeutic claims for drugs.
- 1906** The original **Food and Drugs Act** is passed by Congress on June 30 and signed by President Theodore Roosevelt. It prohibits interstate commerce in misbranded and adulterated foods, drinks and drugs.
- 1911** **U.S. v. Johnson**, the Supreme Court rules that the 1906 Food and Drugs Act does not prohibit false therapeutic claims but only false and misleading statements about the ingredients or identity of a drug.
- 1912** Congress enacts the **Sherley Amendment** to overcome the ruling in *U.S. v. Johnson*. It prohibits labeling medicines with false therapeutic claims intended to defraud the purchaser, a standard difficult to prove.
- 1914** The **Harrison Narcotic Act** requires prescriptions for products exceeding the allowable limit of narcotics and mandates increased record-keeping for physicians and pharmacists who dispense narcotics.
- 1930** The name of the Food, Drug, and Insecticide Administration is shortened to **Food and Drug Administration (FDA)** under an agricultural appropriations act.

1933 FDA recommends a complete revision of the obsolete **1906 Food and Drugs Act**. The first bill is introduced into the Senate, launching a five-year legislative battle.

FDA assembles a graphic display of shortcomings in pharmaceutical and other regulation under the 1906 act. Dubbed by one reporter as the Chamber of Horrors, the display is exhibited nationwide to help draw support for a new law.

1937 **Elixir 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 The **Federal Food, Drug, and Cosmetic (FDC) Act** of 1938 is passed by Congress, containing new provisions

- Extending control to cosmetics and therapeutic devices.
- Requiring new drugs to be shown safe before marketing, starting a new system of drug regulation.
- Eliminating the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases.
- Providing that safe tolerances be set for unavoidable poisonous substances.
- Authorizing standards of identity, quality, and fill-of-container for foods.
- Authorizing factory inspections.
- Adding the remedy of court injunctions to the previous penalties of seizures and prosecutions.

FDA says that sulfanilamide and selected other dangerous drugs must be administered under the direction of a qualified expert, thus launching the **requirement for prescription only (non-narcotic) drugs**.

Under the **Wheeler-Lea Act**, the Federal Trade Commission is charged with overseeing advertising associated with products otherwise regulated by FDA, with the exception of prescription drugs.

1941 **Insulin Amendment** requires FDA to test and certify purity and potency of this lifesaving drug for diabetes.

Nearly 300 deaths and injuries result from distribution of sulfathiazole tablets tainted with the sedative, phenobarbital. The incident prompts FDA to revise manufacturing and quality controls drastically, the beginning of what would later be called **good manufacturing practices (GMPs)**.

1945 **Penicillin Amendment** requires FDA testing and certification of safety and effectiveness of all penicillin products. Later amendments would extend this requirement to all antibiotics. In 1983 such control would be found no longer needed and abolished

- 1948** Supreme Court rules in *U. S. v. Sullivan* that FDA's jurisdiction extends to the retail distribution, thereby permitting FDA to interdict in pharmacies illegal sales of drugs--the most problematical being barbiturates and amphetamines.
- 1950** In *Alberty Food Products Co. v. U.S.*, a court of appeals rules that the directions for use on a drug label must include the purpose for which the drug is offered. Therefore, a worthless remedy cannot escape the law by not stating the condition it is supposed to treat.
- 1951** **Durham-Humphrey Amendment** defines the kinds of drugs that cannot be used safely without medical supervision and restricts their sale to prescription by a licensed practitioner.
- 1952** In *U.S. v. Cardiff*, the Supreme Court rules that the factory inspection provision of the 1938 FDC Act is too vague to be enforced as criminal law.

A nationwide investigation by FDA reveals that chloramphenicol, a broad-spectrum antibiotic, has caused nearly 180 cases of often fatal blood diseases. Two years later FDA would engage the American Society of Hospital Pharmacists, the American Association of Medical Record Librarians, and later the American Medical Association in a **voluntary program of drug reaction reporting**.

- 1953** **Factory Inspection Amendment** clarifies previous law and requires FDA to give manufacturers written reports of conditions observed during inspections and analyses of factory samples.
- 1955** **FDA denies a new drug application** for a cancer drug, Hepasyn, on the grounds that it was not proven safe **because it was not proven effective**, an important consideration for a serious disease in which other useful therapies existed. In 1961 the agency was challenged in a hearing over the same issue involving an antiinfective drug, Altafur, which was decided in FDA's favor.
- 1962** **Thalidomide**, a new sleeping pill, is found to have caused birth defects in thousands of babies born in Western Europe. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, arouse public support for stronger drug regulation.
- Kefauver-Harris Drug Amendments** For the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them.
- 1963** Advisory Committee on Investigational Drugs meets, the **first meeting of a committee to advise FDA** on product approval and policy on an ongoing basis.
- 1965** **Drug Abuse Control Amendments** are enacted to deal with problems caused by abuse of depressants, stimulants, and hallucinogens.

1966 FDA contracts with the National Academy of Sciences/National Research Council to evaluate the **effectiveness of 4,000** drugs approved on the basis of safety alone between 1938 and 1962.

Fair Packaging and Labeling Act requires all consumer products in interstate commerce to be honestly and informatively labeled, with FDA enforcing provisions on foods, drugs, cosmetics, and medical devices.

1968 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.

1970 In **Upjohn v. Finch** the 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.

FDA requires the first **patient package insert** oral contraceptives must contain information for the patient about specific risks and benefits.

The **Comprehensive Drug Abuse Prevention and Control Act** replaces previous laws and categorizes drugs based on abuse and addiction potential compared to their therapeutic value.

1972 **Over-the-Counter Drug Review** begun to enhance the safety, effectiveness and appropriate labeling of drugs sold without prescription.

1973 The **U. S. Supreme Court** upholds the 1962 drug effectiveness law and endorses FDA action to control entire classes of products by regulations rather than to rely only on time-consuming litigation.

1976 **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.

1977 Introduction of the **Bioresearch Monitoring Program** as an agency-wide initiative ensures the quality and integrity of data submitted to FDA and provides for the protection of human subjects in clinical trials by focusing on preclinical studies on animals, clinical investigations, and the work of institutional review boards.

1981 FDA and the Department of Health and Human Services revise **regulations for human subject protections**, based on the 1979 Belmont Report, which had been issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The revised rules provide for wider representation on institutional review boards and they detail elements of what constitutes informed consent, among other provisions.

1982 Tamper-resistant Packaging Regulations issued by FDA to prevent poisonings such as deaths from cyanide placed in Tylenol capsules. The Federal Anti-Tampering Act passed in 1983 makes it a crime to tamper with packaged consumer products.

1983 Orphan Drug Act passed, enabling FDA to promote research and marketing of drugs needed for treating rare diseases.

The first **televised advertisement** for a prescription drug appears in June, purportedly for price comparison with a competitor's product, but it includes information about therapeutic indication and relative value of the advertised drug-without summarized information about side effects. The same year, FDA initiates a **voluntary moratorium on direct-to-consumer advertising** of prescription drugs to study the issue among consumers, health professionals, and industry. FDA withdrew the moratorium in 1985.

1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective. At the same time, the brand-name companies can apply for up to five years additional patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process.

1987 Investigational drug regulations revised to expand access to experimental drugs for patients with serious diseases with no alternative therapies.

1988 Food and Drug Administration Act of 1988 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.

The **Prescription Drug Marketing Act** bans the diversion of prescription drugs from legitimate commercial channels. Congress finds that the resale of such drugs leads to the distribution of mislabeled, adulterated, subpotent, and counterfeit drugs to the public. The new law 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.

1989 The FDA issued guidelines asking manufacturers to determine whether a drug is likely to have **significant use in elderly people** and to include elderly patients in clinical studies if applicable.

1991 Regulations published to **Accelerate the Review of Drugs** for life-threatening diseases.

The policy for protection of human subjects in research, promulgated in 1981 by FDA and the Department of Health and Human Services, is adopted by more than a dozen

federal entities involved in human subject research and becomes known as the **Common Rule**. This rule issues requirements for researchers who obtain and document informed consent, secures special protection for children, women, and prisoners, elaborates on required procedures for institutional review boards, and ensures that research institutions comply with the regulations.

- 1992 Generic Drug Enforcement Act** imposes debarment and other penalties for illegal acts involving abbreviated drug applications.

The U.S. FDA with Japan and Europe establish the **International Conference on Harmonization (ICH)**. The ICH works to reduce the burden of regulation by harmonizing regulatory requirements in the three regions.

Prescription Drug User Fee Act (PDUFA) 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.

- 1993** A consolidation of several adverse reaction reporting systems is launched as **MedWatch**, designed for voluntary reporting of problems associated with medical products to be filed with FDA by health professionals.

Revising a policy from 1977 that excluded women of childbearing potential from early drug studies, FDA issues guidelines calling for improved assessments of **medication responses as a function of gender**. Companies are encouraged to include patients of both sexes in their investigations of drugs and to analyze any gender-specific phenomena.

- 1994 Uruguay Round Agreements Act** extends the patent terms of U.S. drugs from 17 to 20 years.

- 1995** FDA declares **cigarettes** to be "drug delivery devices." Restrictions are proposed on marketing and sales to reduce smoking by young people.

- 1997 Food and Drug Administration Modernization Act (FDAMA)** 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.

- 1998** The **Adverse Event Reporting System (AERS)** is a computerized information database designed to support the FDA's post-marketing safety surveillance program for approved drug and therapeutic biologic products. The ultimate goal of AERS is to improve the public health by providing the best available tools for storing and analyzing safety reports.

The **Demographic Rule** requires that a marketing application analyze data on safety and effectiveness by age, gender, and race.

The **Pediatric Rule** requires manufacturers of selected new and existing drug and biological products to conduct studies to assess their safety and efficacy in children.

The FDA approves the use of **thalidomide** for the treatment of Hansen's Disease, commonly known as leprosy. In tandem with the approval FDA invokes an oversight program designed to help ensure a zero tolerance policy for thalidomide exposure during pregnancy.

1999 **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.

FDA publishes guidances for **electronic submissions** that provide for the receipt and archiving of a new drug application entirely in electronic format without an accompanying paper archival copy.

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. PLEASE VIEW PAGES 11 AND 13.

FDA publishes "**Managing the Risks from Medical Product Use: Creating a Risk Management Framework.**" The report describes current and recommended premarket and postmarket risk assessment procedures and the need for better risk communications.

A Final Guidance for **prescription drug broadcast advertising** is published to ensure consumers get a balanced view of the benefits and risks of a product.

2000 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**.

The U. S. Supreme Court, upholding an earlier decision in Food and Drug Administration v. Brown & Williamson Tobacco Corp. et al., rules 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, that restricted the sale and distribution of cigarettes and smokeless tobacco products to children and adolescents, and that 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.

2002 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.

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. Provisions include a requirement that FDA issue regulations to enhance controls over imported and domestically produced commodities it regulates.

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.

Prescription Drug User Fee Act of 1992 (PDUFA III) receives its third five-year extension. The reauthorization requires pilots for risk management, good review manufacturing practices and a continuous marketing application. PDUFA III continues goals for meetings with industry and to shorten review time.

FDA publishes a guidance for industry that provides advice on establishing registries that monitor the **outcomes of pregnancies** in women exposed to a specific drug.

- 2003** 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.

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.

- 2004** **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.

A ban on over-the-counter steroid precursors, increased penalties for making, selling, or possessing illegal steroids precursors, and funds for preventive education to children are features of the **Anabolic Steroid Control Act of 2004**.

FDA publishes "Innovation or Stagnation? -- Challenge and Opportunity on the Critical Path to New Medical Products." It examines the **critical path** needed to bring therapeutic products to fruition, and how FDA can collaborate to make medical breakthroughs available to those in need as quickly as possible.

Based on results from controlled clinical studies indicating that **Cox-2 selective agents** may be connected to an elevated risk of heart attack and stroke, FDA issues a public health advisory urging health professionals to limit the use of these drugs.

FDA regulation calls for over-the-counter medicines commonly used in hospitals and all prescription medicines to have a **bar code**. The bar code rule aims to protect patients from preventable medication errors.

2005 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.

Three final guidances were published to fulfill FDA's commitment to the **risk management performance goals** that are part of the 2002 reauthorization of PDUFA.

- Premarketing Risk Assessment
- Development and Use of Risk Minimization Action Plans
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

2006 FDA approves final rule, **Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products**. New content and format requirements make it easier for healthcare professionals to access, read, and use information in FDA-approved labeling.