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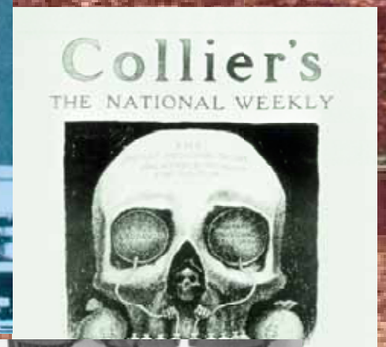

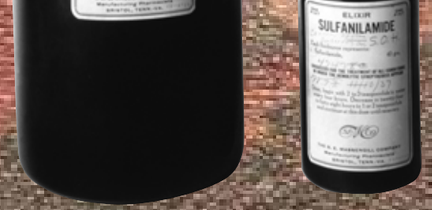

The History of Drug Regulation in the United States

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

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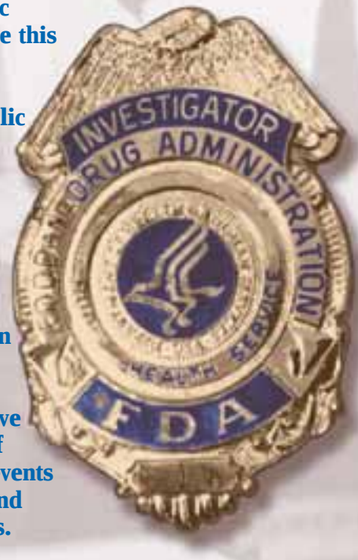
The History of Drug Regulation

The U. S. Food and Drug Administration, the oldest federal agency dedicated to consumer protection, is a scientific, regulatory, and public health agency that oversees items accounting for 25 cents of every dollar spent by consumers. Its jurisdiction encompasses most food products (other than meat and poultry), human and animal drugs, therapeutic agents of biological origin, medical devices, radiation-emitting products for consumer and professional use, cosmetics, and animal feed. Originating as a single chemist appointed to the U. S. Department of Agriculture in 1862, FDA's modern era as a consumer protection agency began with the passage of the Pure Food and Drugs Act in 1906. The FDA in 2006 employs more than 10,000 chemists, pharmacologists, physicians, microbiologists, pharmacists, veterinarians, lawyers, and others, with a budget of $1.83 billion.

The challenge of providing the American public with safe and effective medicines has grown in concert with the expansion of the drug armamentarium over the 20th century--the "chemotherapeutic revolution." While this revolution has unquestionably enhanced the public health, it has not been a phenomenon of unimpeded progress and improvement in the public health. Indeed, changes in the way this country regulates drugs typically have been borne out of adversity, out of events that have killed and injured thousands.



This historical overview will discuss the evolution of the current drug regulatory system, recognized globally as the gold standard for drug safety and efficacy. The regulation of drugs in America is anchored in landmark legislation during the Progressive Era, the New Deal, and the New Frontier, though other noteworthy developments in this area have emerged in the past 150 years. In addition to the key laws, their enforcement by the FDA will be emphasized. Also, this story will examine how the legislative and judicial branches of government, regulated interests, consumers and their representatives, and the media all played a role in the evolution of this system.

A Bureau of Chemistry laboratory, c. 1910

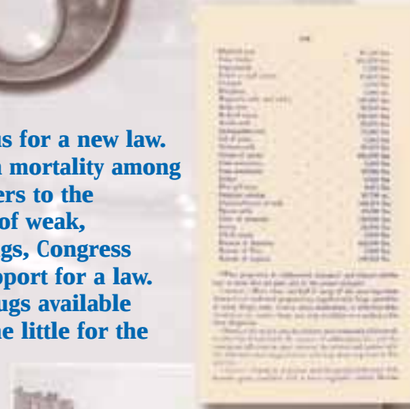
The badge of the Associate Commissioner for Regulatory Affairs, the chief enforcement officer of FDA

1848

Imported Drugs

With a fledgling domestic industry, the drug supply in 19th century America depended largely on imports. But as the health sciences, professions, institutions, and legal framework in the U. S. lagged noticeably behind European nations, America became a dumping ground for adulterated drugs. British statesman and prominent pharmacist Jacob Bell noted that manufacturers understood that drugs reduced by decay or ingenuity were still "good enough for America." A concern for drug quality led to the establishment of the first pharmacy schools in this country and the publication of the *United States Pharmacopoeia*, all in the 1820s.

Two developments in the 1840s facilitated a legislative response to the problem. First, Lewis Caleb Beck's *Adulteration of Various Substances Used in Medicine and the Arts* (1846) provided ample documentation of the problems in the American drug market. Second, the Mexican-American War of 1846-1848 provided a political impetus for a new law. Attributing high mortality among American soldiers to the administration of weak, adulterated drugs, Congress whipped up support for a law. In truth, the drugs available would have done little for the yellow fever, cholera, dysentery, and other responsible ailments. The blame should have been fixed on the insanitary camp conditions and poor nutrition.



The Drug Importation Act, signed by President James K. Polk on June 26, 1848, prohibited the importation of unsafe or adulterated drugs, enforced by a cadre of inspectors stationed at key ports of entry. While the law worked well at first, inspector appointments soon were made on the basis of political spoils rather than qualifications. In addition, the law did not address the proliferating problem of domestic patent medicines. According to eminent physician and pharmacist Edward R. Squibb, the Drug Importation Act was a dead letter by the beginning of the Civil War.

Opium, derived from Papaver somniferum, provided at least symptomatic relief at this time--if it were not too debased

Cantharides (Spanish flies), used chiefly as a blistering agent at this time, was adulterated with other insects and even beads

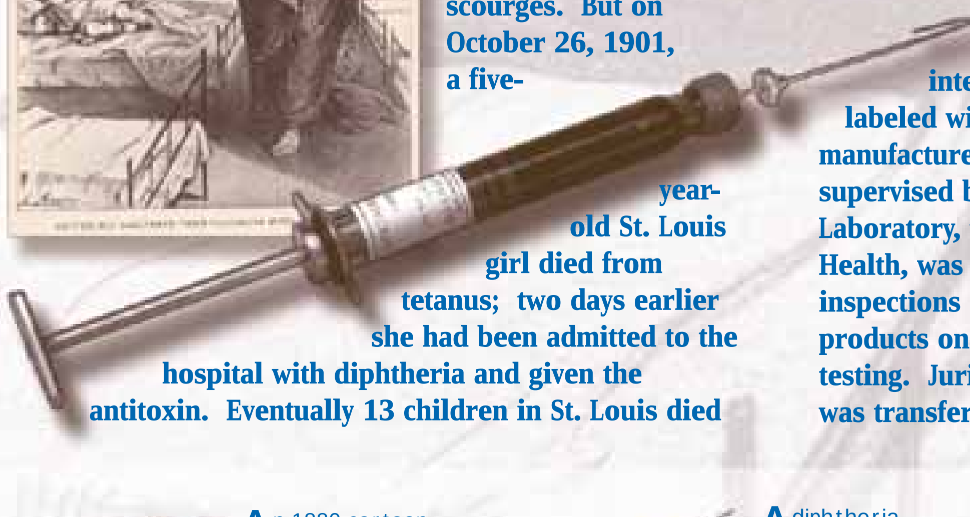
The Transactions of the American Medical Association recognized the growing problem of adulterated drugs

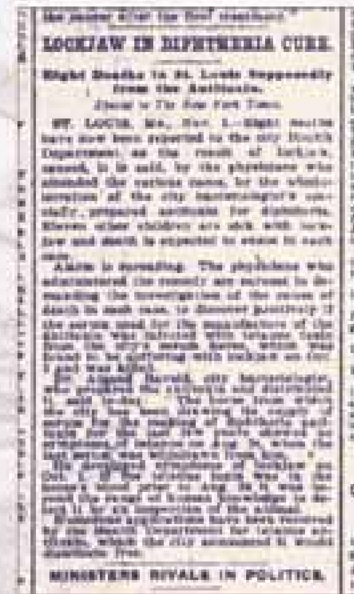
General Winfield Scott and his troops entering Mexico City in 1847 (Chicago Historical Society)

1902 Biological Therapeutics

In 1890 Emil von Behring and Shibasaburo Kitasato in Berlin drew on work about the nature of immunity and the specific character of diphtheria when they discovered an effective antitoxin for diphtheria from blood serum of animals injected with diphtheria toxin. That effort, the identification of nearly two dozen pathogens responsible for specific diseases from 1880 to 1900, and the subsequent discovery of various strains of pathogens, launched a wave of interest to control infectious diseases through so-called serum therapy. With varying degrees of success, researchers used serums against tetanus, typhoid, rabies, pneumonia, meningitis, and other diseases.

Americans, led by public health laboratories, quickly adopted the techniques for producing cures for diphtheria and other scourges. But on October 26, 1901, a five-year-old St. Louis girl died from tetanus; two days earlier she had been admitted to the hospital with diphtheria and given the antitoxin. Eventually 13 children in St. Louis died of tetanus, and the cause was traced to a supply of diphtheria antitoxin prepared by the St. Louis Board of Health from a tetanus-infected horse. Although the St. Louis disaster was the worst, it wasn't the only such incident in the United States and Europe. Camden, New Jersey, was the site of almost a hundred cases of post-vaccination tetanus, including the deaths of nine children, in the Fall of 1901. The likely source was a commercial concern.




LOCKJAW IN DIPHTHERIA CURE.
Eight Deaths in St. Louis Supposedly from the Antitoxin.
MINISTERS RIVALS IN POLITICS

These events spurred action in Congress, and the Biologics Control Act of July 1, 1902, was passed quickly and without any notable opposition. The act mandated annual licensing of establishments to manufacture and sell vaccines, sera, antitoxins, and similar products in interstate commerce. Biologics had to be labeled with the name and license number of the manufacturer, and the production had to be supervised by a qualified scientist. The Hygienic Laboratory, forerunner of the National Institutes of Health, was authorized to conduct regular inspections of the establishments and to sample products on the open market for purity and potency testing. Jurisdiction over biological therapeutics was transferred to FDA in 1972.

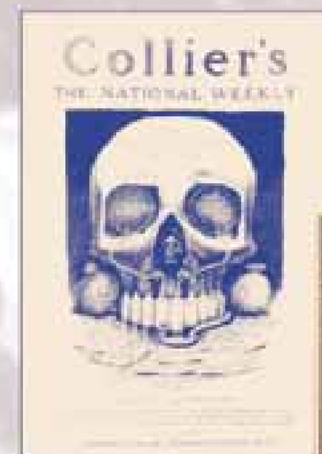

An 1880 cartoon from *Puck* warning about vaccination (William Helfand)


A diphtheria antitoxin syringe from Eli Lilly & Co.


A tetanus outbreak in St. Louis helped lead to federal controls

1906 Labeling Drugs

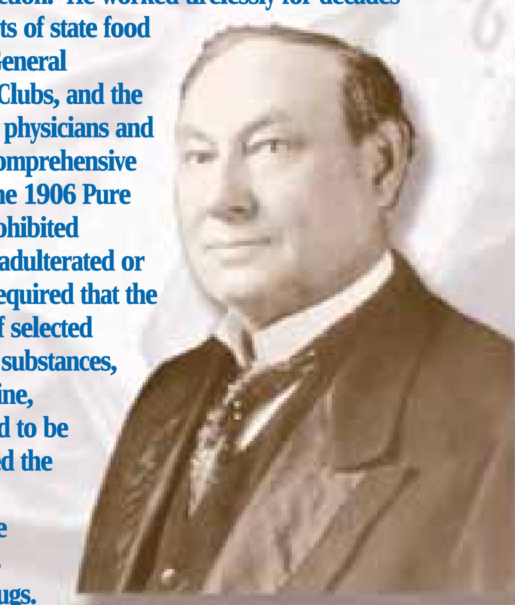
The food and drug marketplace was so corrupt that some states began to hire their own chemists to certify the quality and purity of foods and drugs sold within their states, and to defend against the sale of adulterated and inferior foods and drugs from outside. A few states passed sweeping laws, but there was little agreement on standards for foods and drugs. In addition, these laws typically punished retailers, but manufacturers were the greater problem.



Companies wielded substantial influence, especially those in the patent medicine industry. There was little to stop patent medicine makers from claiming anything and putting anything in their products. In fact, by the 1890s patent medicine manufacturers used so-called "red clauses" in their advertising contracts with newspapers and magazines. These muzzle clauses voided the contract if a state law regulating nostrums were passed. Thus, not only were many editorials silent on the need for such laws, they actively campaigned against them.

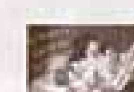
But the nostrum makers weren't able to stifle the *entire* fourth estate. A few muckraking journalists helped expose the red clauses, the false testimonials, the nostrums laden with arsenic and other harmful ingredients, the unfounded cures for cancer, tuberculosis, syphilis, narcotic addiction, and a host of other serious as well as self-limited diseases. The most influential work in this genre was the series by Samuel Hopkins Adams that appeared in *Collier's* on October 7, 1905, entitled "The Great American Fraud." Analogously, Upton Sinclair's novel, *The Jungle*, exposed egregious offenses in the food industry.

More than anyone else, Harvey Wiley, head of the Bureau of Chemistry of the U. S. Department of Agriculture, led the way toward consumer protection. He worked tirelessly for decades to amalgamate the efforts of state food and drug officials, the General Federation of Women's Clubs, and the national associations of physicians and pharmacists toward a comprehensive federal law. That law, the 1906 Pure Food and Drugs Act, prohibited interstate commerce in adulterated or misbranded drugs; it required that the presence and amount of selected dangerous or addicting substances, such as alcohol, morphine, heroin, and cocaine, had to be labeled; and it identified the *United States Pharmacopoeia* and the *National Formulary* as official standards for drugs.




Collier's used this image to announce its upcoming series on patent medicines by Adams


Patent medicines such as Peter's Specific claimed much but divulged little if any of its contents, quite legally, pre-1906


Mrs. Winslow's Soothing Syrup for teething and colicky babies, unlabeled yet laced with morphine, killed many infants


Harvey Washington Wiley, widely recognized as the father of the FDA

1938 Drug Safety


TWO MORE DEATHS HERE MAY BE DUE TO USE OF ELIXIR

Both Patients Were Treated for Infections — One Victim Was East St. Louisan

Important as it was, the 1906 act was rife with shortcomings, such as its failure to regulate medical devices or cosmetics, the lack of explicit authority to conduct factory inspections, the difficulty in prosecuting false therapeutic claims following a 1911 Supreme Court ruling, and the inability to control what drugs could be marketed. The S. E. Massengill Company bore out the truth of the last shortcoming when they introduced Elixir Sulfanilamide in September 1937. This attempt to introduce a flavorful oral dosage form of the new antiinfective wonder drug was a disaster. The firm used an untested solvent, diethylene glycol, which is chemically related to antifreeze. By the time FDA became aware of the problem and removed the product from pharmacy shelves and medicine cabinets around the country, the preparation had caused 107 deaths, including many children. The firm, whose president maintained that the deaths were due to idiosyncratic reactions to the sulfa drug, could be prosecuted only for distributing a misbranded drug; an "elixir" had to contain alcohol as a solvent.

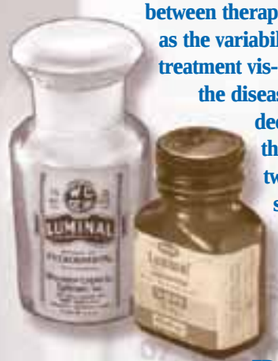
The Elixir Sulfanilamide disaster reinvigorated a bill to replace the 1906 act that had been languishing in Congress since 1933. Further refined, President Roosevelt signed the Food, Drug, and Cosmetic Act into law on June 25, 1938. Among many other provisions, the 1938 act required that firms had to prove to FDA that any new drug was safe before it could be marketed: the birth of the new drug application. The new law covered cosmetics and medical devices, authorized factory inspections, and outlawed bogus therapeutic claims for drugs. A separate law brought drug advertising under the Federal Trade Commission's jurisdiction. The law recognized the problem of squaring the desire of consumers to pursue self-medication with the introduction of potent and effective new drugs, such as the sulfonamides. Thus drugs had to bear adequate directions for safe use, which included warnings whenever necessary.

Massengill's Elixir Sulfanilamide, a 1937 therapeutic disaster

One result of the 1937 incident was more cautious labeling

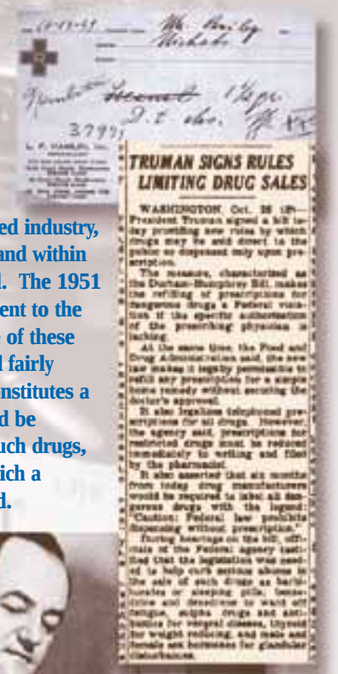
Products that contained the laxative, phenolphthalein, were among those requiring detailed warnings for informed consumer use

1951 Prescriptions



With some potent drugs, the thin margin of error between therapeutic and adverse effects, as well as the variability of dosage or duration of treatment vis-à-vis the individual patient and the disease treated, required informed decisions in drug therapy. With this in mind, the FDA ruled within two months of the 1938 act that some drugs simply could not be labeled for safe use. Rather, they required medical supervision for individualized directions for use, and had to be labeled accordingly. By 1941 FDA identified over 20 drugs or drug groups that had to be appropriately labeled and sold only through a physician or dentist's prescription, such as sulfas, barbiturates, amphetamines, and thyroid.

Illegal sales of dangerous drugs--the vast majority of problems involving barbiturates and amphetamines--occupied more drug regulatory time at FDA than all other drug problems combined from the 1940s to the mid-1960s. Early on, unlawful over-the-counter sales and unauthorized prescription refills in pharmacies were the principal sources for illegal direct-to-consumer sales. Pharmacies were indeed responsible for most of the illicitly acquired amphetamines and barbiturates, but they were not the only source. Sloppy prescribing habits shared some of the blame. Also, from the early 1950s on, sales through nontraditional channels--truck stops, bars, cafes, individual peddlers, and other venues--increasingly contributed to illegal distribution.


TRUMAN SIGNS RULES LIMITING DRUG SALES

WASHINGTON, Oct. 26 (AP)—President Truman signed a bill today prohibiting new rules by which drugs may be sold direct to the public or dispensed only upon prescription.

The measure, characterized as the Durham-Humphrey Bill, makes the refilling of prescriptions for dangerous drugs a Federal violation if the specific authorizations of the prescribing physician is lacking.

At the same time, the Food and Drug Administration said the new law makes it legally permissible to refill any prescription for a simple home remedy without securing the doctor's approval.

It also legalizes telephoned prescriptions for all drugs. However, the agency said, prescriptions for restricted drugs must be reduced immediately to writing and filed by the pharmacist.

It also asserted that six months from today drug manufacturers would be required to label all dangerous drugs with the legend: "Caution: Federal law prohibits dispensing without prescription."

The first act was vague on issues such as what a prescription was and who would be responsible for identifying prescription versus non-prescription drugs. This lack of statutory direction created many battles between FDA, regulated industry, and professional pharmacy, and within some of these groups as well. The 1951 Durham-Humphrey Amendment to the 1938 act helped clarify some of these disputed issues. It identified fairly clear parameters for what constitutes a prescription drug, who would be responsible for identifying such drugs, and the conditions under which a prescription could be refilled.

Example of labeling before 1938 and after 1951; note the warning statement and prescription legend on the sample at right

A manufacturer elects to remind pharmacists that prescription drugs require prescriber authorization for sale

The names of pharmacists Senator Hubert Humphrey, pictured here, and Representative Carl Durham appropriately headed the 1951 prescription law

1962 Drug Efficacy

A push for revisions of the drug statutes emerged from hearings into the practices of the pharmaceutical industry by Senator Estes Kefauver of Tennessee, which began in 1959. Though the Kefauver hearings started out as an investigation of the cost of medicines in America, other issues soon came under scrutiny, such as advertising abuses, questionable efficacy of drugs, and the lack of regulation in these areas. But as was the case with the 1902 and 1938 laws, a therapeutic disaster laid bare the need for new legislation. On September 12, 1960, an American licensee, the William S. Merrell Company of Cincinnati, submitted to FDA a new drug application for Kevadon, the brand name of a sedative that had been marketed in Europe since 1956: thalidomide. The FDA medical officer in charge of this review, Frances Kelsey, believed the data were incomplete to support the safety of this drug.

The firm continued to pressure Kelsey and the agency to approve the application--until November 1961, when the drug was pulled off the German market because of its association with grave congenital abnormalities. Several thousand newborns in Europe and elsewhere suffered the teratogenic effects of thalidomide. Though the drug was never approved in this country, the firm distributed Kevadon to over 1,000 physicians under the guise of investigational use. Over 20,000 Americans received thalidomide in this "study," including 624 pregnant patients, and about 17 known newborns suffered the effects of the drug.

The thalidomide tragedy resurrected Kefauver's bill to enhance drug regulation that had stalled in Congress, and the Kefauver-Harris Amendments became law on October 10, 1962. Manufacturers henceforth had to prove to FDA that their drugs were effective as well as safe before they could go on the market. Control over clinical investigations--including a requirement for informed consent--was placed on a firm statutory basis. FDA received authority to regulate advertising of prescription drugs, establish good manufacturing practices as a means to promote quality assurance, and access certain company control and production records to verify production procedures. Finally, the law required that all drugs introduced between 1938 and 1962 had to be effective. An FDA-National Academy of Sciences collaborative study showed that nearly 40 percent of these products were not effective. A similarly comprehensive study of over-the-counter products began ten years later.


The Detroit Free Press

Issues Thalidomide Warning

KENNEDY ASKS DRUG CURBS

President Kennedy signs the Kefauver-Harris new drug amendments into law on October 10, 1962, as Dr. Kelsey, Sen. Kefauver, and others look on

Senator Estes Kefauver of Tennessee, whose hearings initiated a movement that resulted in the new drug amendments

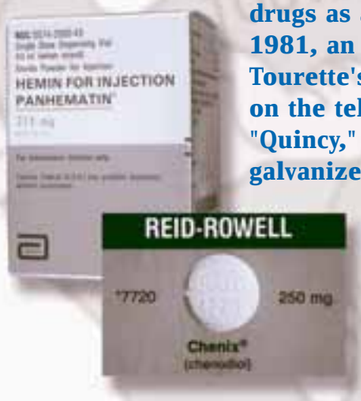
President Kennedy confers on Dr. Frances Kelsey the highest recognition possible for federal civilian service in 1962 for her thalidomide work

thalidomide, responsible for thousands of birth defects in the 1950s and 1960s, recaptured therapeutic interest in the 1990s

1983 Rare Diseases

The early 1980s witnessed the confluence of several different interests on a public health issue that theretofore had received little attention: orphan diseases, serious and debilitating rare diseases affecting less than 200,000 people, which typically receive little funding toward their prevention or treatment. About 20 million Americans suffer from at least one of the more than 5000 known rare diseases. Representative Henry Waxman of California initiated hearings into the lack of drugs for orphan diseases. Also, health care providers, researchers, and patient advocacy groups--especially the National Organization for Rare Disorders--promoted the development of orphan drugs as a public issue. In 1981, an episode about Tourette's syndrome aired on the television series, "Quincy," which helped galvanize public support, too. The Orphan Drug Act finally became law in 1983.

Since pharmaceutical companies had been reluctant to develop treatments for these diseases because there was little chance of recovering their research investments, the law was crafted to induce industry's interest. In the case of an unprofitable or unpatentable drug targeted for a patient population of less than 200,000, the manufacturer would receive development grants, assistance from FDA in planning its animal and clinical protocols, 50 percent tax credits for clinical investigation expenses, and a seven-year monopoly to market the drug. Over 700 drugs have received orphan designation so far.



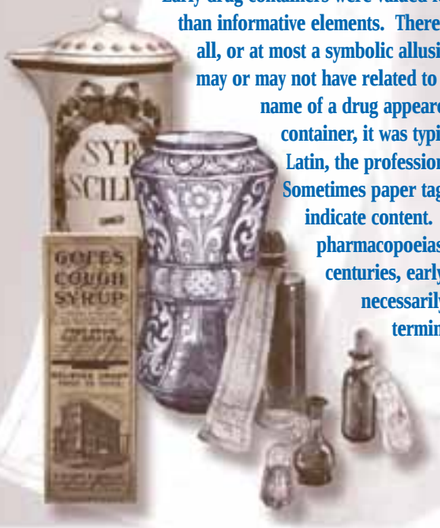
FDA is just one of several government agencies that have a role in the battle against rare diseases

Hemin (Panhematin) and chenodiol (Chenix) were the first two orphan drugs recognized under the 1983 Orphan Drugs Act

Label Evolution I

In the history of non-narcotic drug control in this country, legislation and regulations have addressed pharmaceuticals on many different fronts to protect the consumer, from testing and manufacture to advertising and distribution. One area of regulatory concern has focused on the principal source of drug information for the physician, pharmacist, and consumer, the drug label. Drug labeling today conveys a vast array of information about indications, dosage, untoward reactions, and other elements, but there was a time when the consumer had no idea what was in a pharmaceutical product, much less what it might do.

Early drug containers were valued for decorative rather than informative elements. There might be no label at all, or at most a symbolic allusion to an entity that may or may not have related to health. When the name of a drug appeared on a drug container, it was typically abbreviated in Latin, the professional vernacular. Sometimes paper tags were attached to indicate content. Though pharmacopoeias have existed for centuries, early drug jars did not necessarily have a standard terminology.



In the U. S., there was no federal check on what drugs could contain or claim before 1906. But the 1906 act, principally a labeling law, mandated a variety of information on the drug package. The provision for labeling 11 dangerous ingredients led many patent medicine makers to reformulate their products to avoid honest (and possibly embarrassing) labeling; some simply went out of business. While the 1906 act identified the *United States Pharmacopoeia* and the *National Formulary* as the official compendia for drug standards, the law permitted the marketing of nonstandard drugs as long as the label stated the specific variation from the standard.

Manufacturers or wholesalers could label their drugs or foods with a guarantee that the article complied with the law, exempting the retailer from prosecution under the 1906 act. The original version of the guarantee stated, "Guaranteed under the Food and Drugs Act, June 30, 1906." However, some manufacturers advertised the guarantee as a government endorsement. A revised guarantee in December 1908 read, "Guaranteed by [name of guarantor] under the Food and Drugs Act, June 30, 1906." Convinced that the public continued to be misled, the government abandoned the labeled guarantee in 1918.

When early containers included drug names, such as this late 18th century Viennese syrup jar, the name was abbreviated in Latin (AIHP)

This 16th century German drug jar exemplifies early drug containers that were more aesthetic than informative (AIHP)

Some firms used the original (left) and revised guarantee to claim government endorsement of their products

Some post-1906 medicines emphasized the fact that they did not possess any dangerous or addictive substances

Examples of 18th century drug containers with information attached

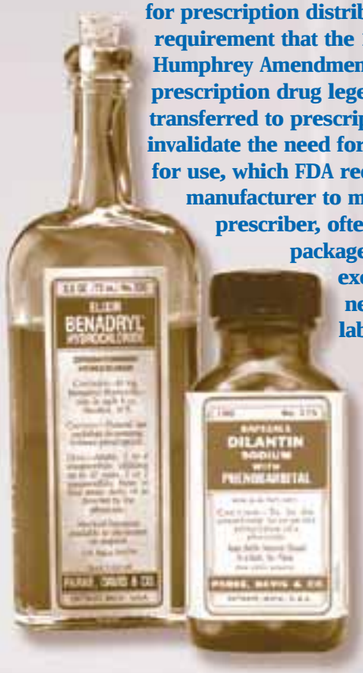
The American Medical Association employed a voluntary system of drug approval since 1905, which included a labeled AMA seal

The variation clause in the 1906 act permitted nonstandard drugs to remain on the market -- as long as the variances were stated

Label Evolution II

The 1938 law improved on many of the labeling shortcomings of the 1906 act. For example, it mandated complete listing of ingredients, and it required that drugs be labeled with adequate directions for safe use. The adequate directions mandate affected both the consumer and the prescriber. By 1940 FDA had developed over two dozen warning statements for different drugs intended for sale directly to the public. The agency's decision in 1938 that some drugs simply were too dangerous for labeled directions to the consumer led to the requirement that such drugs be labeled for prescription distribution only, a requirement that the 1951 Durham-Humphrey Amendment codified as the prescription drug legend. That a drug was transferred to prescription use did not invalidate the need for adequate directions for use, which FDA required the manufacturer to make available to the prescriber, often in the form of a package insert. The law exempted investigational new drugs from these labeling provisions.

Most of the basics of a drug label--such as the listing of ingredients and directions for the patient and prescriber--were established in the first half of the century, but that is not to say the latter half of the century has been without important developments. Consumer information on both over-the-counter and prescription drugs has increased substantially over the past few decades. In 1970 FDA issued regulations requiring oral contraceptives to provide patients with information about their use--the beginning of patient package inserts for prescription drugs. In 1995 FDA announced a program to provide patients with more information about prescription drugs with significant risks through standardized literature, or "medguides," provided by pharmacists. In 1994 the agency introduced prototypes for over-the-counter drug labels in an easy-to-read format.



The early prescription legend emerged in 1938 via regulation (left), and it was altered slightly by statute in 1951

Enhanced patient information arrived in 1970 with the patient package insert for oral contraceptives

Since the turn of the century, the drug label has undergone a metamorphosis of information

Even prescription drugs had to include information for doctors about the dosage, pharmacology, and other key characteristics

DRUG Approval In The 1990's

The standard drug testing and approval process today involves several stages. First, pre-clinical research and development--including animal testing--can take from one to three years. Next, once a firm files an investigational new drug application with FDA, phase 1 clinical studies proceed to examine the drug's toxicity and pharmacology in 20 to 100 volunteers, and this stage requires several months. Then the drug is tested in larger groups of patients who have the disease the drug is intended to treat. Phase 2 clinical studies, with as many as several hundred patients, last from several months to two years. Phase 3 investigates the drug in several hundred to several thousand patients for one to four years. Then the results, in the form of a new drug application, are reviewed by FDA over an average of about two years. Advisory committees of scientists, health care professionals, and consumer representatives outside the agency consult on drug reviews, but the final decision rests with FDA. If the agency approves the drug, post-marketing surveillance will continue after the medicine is on the market. Of every 100 drugs that begin the investigational process, about 20 will be approved by the agency.

In the last two decades there have been several significant changes to the drug approval process. For example, treatment INDs (1987) expand patient access to experimental drugs for serious diseases with no alternative therapies. Accelerated approval mechanisms (1988-1992), including study designs developed by the sponsor with FDA, speed approval of drugs for life-threatening diseases based on findings that predict therapeutic benefit, though the drug sponsor must continue studies on actual clinical benefits. Parallel track investigations (1992) make experimental drugs more widely available to HIV patients while controlled trials of the drugs continue. As much as any interest group, the community of patients, families, and others affected by HIV and AIDS have actively engaged the agency in drug approval policies.

The Prescription Drug User Fee Act of 1992 provides for sponsor support of drug review and ancillary expenses toward speedier evaluation of new drug and biologic applications and elimination of the backlog of pending applications. The combination of adding drug review staff through user fees and streamlining review procedures independently of the 1992 law have reduced approval times significantly. Drugs for serious and life-threatening diseases such as cancer and AIDS now are approved typically in less than six months, and sometimes in a few weeks. The agency's drug review improvements were recognized in October 1997 by the John F. Kennedy School of Government of Harvard University with the Innovations in American Government Award.

An FDA medical officer (at lectern) briefs the Oncologic Drugs Advisory Committee about a drug being considered for approval

A 1988 protest at FDA headquarters in Rockville, Maryland, organized by the AIDS Coalition to Unleash Power (ACT-UP)

An FDA review official enveloped by safety and efficacy data

DRUG Approval In The 21st Century

FDA began work in the 1990s to develop standards for the exchange of electronic information critical to the agency's mission. This recognized both the inefficiency of paper for transferring mass quantities of data and the need to develop a harmonized format that would be usable by FDA as well as its counterparts in the European Union and Japan. Consequently, firms are now able to submit paperless product applications and related material to world regulatory agencies more efficiently, while each review authority maintains its own high standards for product evaluation.

Because all drugs have some risk, a 1999 FDA task force advised the agency to make more systematic use of the principles of risk management in the way FDA oversees drug development and marketing. Following this recommendation, FDA implemented a model for risk management that identifies the risks at stake when using a drug, finds ways to minimize them, conveys information to those affected, and oversees how effectively risks are being contained. While there is no such thing as risk-free drug therapy, this approach to drug regulation will help reduce the potential harm to the patient.

Despite various reforms to FDA's processes, developing new medicines has become increasingly expensive and time-consuming. The Critical Path Initiative is FDA's effort to address the need for up-to-date scientific means of evaluating the safety, efficacy, and quality of medicines. The object of this initiative is to reduce the time, cost, and uncertainty of product development.

FDA's consumer education public service announcement on risk management

Electronic submissions enabled the agency to exchange mass quantities of data efficiently between drug reviewers and industry

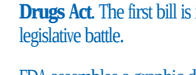
In 1999 FDA published the final regulation requiring all over-the-counter drug products to carry clear, simple, and readable labeling in a standardized format

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. *Please View Page 3.*

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. *Please View Page 4.*



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. *Please View Page 5, and Page 11.*

1911 In **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**. *Please View Page 6.*

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. *Please View Page 7.*

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. *Please View Page 8.*

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. *Please View Page 8.*

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. *Please View Page 11.*

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.

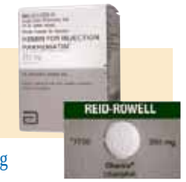
1976 **Vitamins and Minerals Amendments** ("Proxmire Amendments") stop FDA from establishing standards limiting potency of vitamins and minerals in food supplements or regulating them as drugs based solely on potency.

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. *Please View Page 9.*



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. *Please View Page 12.*

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. *Please View Page 12.*

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. *Please View Page 12.*

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. *Please View Page 8.*

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. *Please View Page 13.*

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

Please View Page 13.

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.

Dr. Harvey W. Wiley (in top hat), "Father of the Pure Food and Drugs Act," stands on the steps of the Bureau of Chemistry building in Washington D.C., as it was at the time of the 1906 Act.

By the year 2010, the Food and Drug Administration (FDA) plans to complete consolidation of most of its operations in newly constructed buildings at the White Oak campus in Montgomery County, MD.