

## DRUGS THAT SHAPED THE FDA: FROM ELIXIR SULFANILAMIDE TO THALIDOMIDE

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Jessica Epstein, Saint Peter's University, 2641 Kennedy Boulevard, Jersey City, NJ 07306;  
jepstein1@saintpeters.edu

### Introduction

The United States Food and Drug Administration (FDA) currently regulates pharmaceuticals, medical devices and food products. Since the inception of the FDA in 1906, two key pieces of legislation have shaped the FDA into the organization that we recognize today: The Federal Food, Drug and Cosmetic Act (FD&C Act) of 1938 and the Kefauver-Harris amendment in 1962. The FD&C Act of 1938 gave the FDA authority to oversee the safety of food, drugs and cosmetics. The law authorized the FDA to require evidence of safety for new drugs, issue standards for food, and conduct factory inspections. The Kefauver-Harris amendment to the FD&C Act in 1962 required each new drug application (NDA) contain evidence from “adequate and well-controlled studies” demonstrating that a new drug was effective for its intended use and that the established benefits of the drug outweighed its known risks. Companies were required to present animal studies to the FDA *before* obtaining approval to test on humans. Furthermore, clinical studies on humans required informed consent from participants. Each of these pieces of legislation dramatically shaped the FDA and the pharmaceutical industry in the United States (US). They were the product of mounting consumer activism and political pressure, and they were ultimately pushed to passage by high-profile medical disasters: elixir sulfanilamide in 1937 and thalidomide in 1962.

### Background

Throughout human history, humans have altered food to prevent spoilage and improve taste (1). As early as Colonial times, lawmakers enacted statutes to protect the health and money of citizens. In the early United States and even earlier, in Colonial times, states and towns sporadically enacted food safety and consumer protection laws. For example, in 1720 Massachusetts outlawed the substitution in bread of “any other grain” than whatever local regulation specified (2). It was not until the Mexican War and a crisis over medications for the troops, that Congress enacted federal legislation to ban adulterated imported drugs. The Drug Importation Act of 1848 required the inspection of imported drugs and medical preparations (3). The problem of food and drug adulteration was already well established in England. In 1820 Friedrich Accum, a German scientist living in London, published, *A Treatise on Adulteration of Food and Culinary Poisons* (4). Accum used analytical techniques to uncover the use of poisonous substances in food and was the first person to reach a wide audience.

During the second half of the 19<sup>th</sup> century, the US economy witnessed a dramatic shift from agriculture to industry (5). Locally produced goods were shipped to factories to be preserved, packaged and sold to a growing urban population. With an expanded distribution network, manufacturers no longer interacted directly with their customers and adulteration and deception became more

common and profitable (1). In the US, the most common food adulteration took the form of chemicals to preserve food, hide signs of spoiled food and change a food's color or texture. Examples included the use of copper sulfate to make faded vegetables green, sodium benzoate as a preservative, or borax to make odorous ham acceptable when canned. In other cases, the ingredients were misleading; for example, hayseeds and some apple skins could transform glucose into a substance resembling "strawberry jam" (1).

By the second half of the 19<sup>th</sup> century there was also a booming "patent" medicines industry in the US. The medicines typically consisted of standard remedies used by doctors at the time. There were often multiple ingredients, and they were sold on the basis of attractive packaging and testimonials that someone claimed to be completely cured by this medicine. The medicine itself was seldom patented, but rather the trademarked labels and shape of the bottle were used to appeal to illiterate consumers. Many products contained alcohol, and some patent medicines contained highly addictive substances such as opium (6).

Although, there were attempts at regulation since colonial times, a well organized push for comprehensive food and drug regulation in the US began during the Progressive Era as activists and political reformers sought to use the federal government to counteract the negative social consequences of industrialization (7). In 1902 Congress passed the Biologics Control Act after the St. Louis Health Department prepared diphtheria antitoxin contaminated with tetanus and thirteen children died (8, 9). In 1906, the Pure Food and Drug Act was passed. The Pure Food and Drug Act established federal government oversight for "preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs or medicines, and liquors" (10). Enforcement fell under the purview of the Bureau of Chemistry in the US Department of Agriculture (USDA), which later became the FDA in 1930. There were weaknesses in the language of the law and Congress did not authorize money for enforcement. But the law did establish, for the first time in US history, that the federal government would oversee commercial abuses and that patent medicines should be considered drugs.

### The American Chamber of Horrors

The Pure Food and Drug Act of 1906 was tested many times. In order to be removed from the market, false claims and dangerous products needed to be prosecuted

in court. An early challenge to drug regulation came in 1908 when the government seized a large quantity of a product called Johnson's Mild Combination Treatment for Cancer. In *U.S. v. Johnson*, the Supreme Court ruled against the government, finding that the product's false claims for effectiveness were not within the scope of the Pure Food and Drug Act (11, 12). The challenge with this case and many others was that the bureau had to demonstrate *intent* by the manufacturer to deceive the consumer. For consumer advocates trying to effect change, it made more sense to prohibit the marketing of toxic or ineffective drugs prior to public consumption, rather than trying to retroactively remove one that proved unsafe or misleading.

**CANCER CAN BE CURED**

I WANT TO SEND TO ALL SUFFERERS FROM CANCER, THESE TWO BIG BOOKS ABSOLUTELY FREE

and these statements prove it

Back of Every Statement I make is the Word of Living Hundreds Who Have Used My Mild Combination Treatment.

Read the Proof

DR. JOHNSON REMEDY CO. Dr. S. A. Mose Kansas City, Mo.

Figure 1. Advertisements like this one promoted a cure for cancer (13). At the time, the Bureau of Chemistry had to demonstrate that the manufacturer intended to deceive in order to remove unsafe or ineffective products.

Starting in 1912, FDA officials began to assemble a collection of some of the most egregious products, later named, "The American Chamber of Horrors," by a reporter (14, 15). The exhibit was hardly gruesome, but did contain well-documented examples of manufacturer mislabeling and adulteration of food products. The American Chamber of Horrors was initially an exhibit for Congress, but the 1933 publication of *One Hundred Million Guinea Pigs* by Arthur Kallet and Frederick Schlink (16) brought the exhibit to the public's attention. Some companies changed their production practices in order to be removed from the exhibit.

In addition to the American Chamber of Horrors, the FDA drew upon support from women's groups and organized consumer unions: The General Federation of Women's Clubs (GFWC), the Women's Christian

Temperance Union (WCTU) and Consumers' Research (CR) which were some of the most powerful lobbying organizations at the time (17). In the spring of 1933, FDA commissioner, Walter Campbell, and Paul Dunbar teamed up with Rexford Tugwell, the Assistant Secretary of Agriculture, to draft new legislation (7, 18)

New York Senator Royal Copeland introduced the bill, S1944, to Congress in December of 1933 (19). The bill was an attempt to regulate patent medicines and required manufacturers to apply labels disclosing ingredients. The FDA would have the power to seize misbranded goods and no longer had to prove intent to defraud. The bill also held manufacturers and advertisers legally liable for fraudulent claims (20). The affected industries mounted a well-organized opposition, claiming that Americans have the right to self medicate. Although several factors seemed favorable for the bill to pass (a Democratic Congress and President), the legislation languished in Congress for another five years (7) until the Massengill Company introduced elixir sulfanilamide.

### Elixir Sulfanilamide

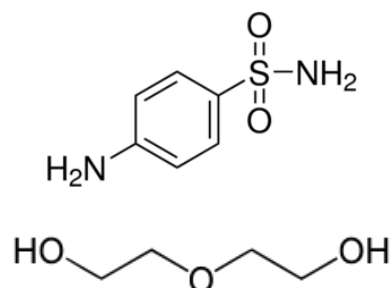
In his book *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*, Daniel Carpenter discusses the concepts of "policy tragedy" and "political framing" (17)

In a policy tragedy, someone has been harmed, and wrongly so. The "victim" may be an individual or collective, and the latter is often represented by the former in the manner of an exemplar or "poster child." A culprit (often the system) is responsible in a causal, nearly criminal fashion. The public points a finger at essential and observable features of the regulatory regime, the status quo, as causing or failing to prevent the harm or injustice in question. Yet in a policy tragedy, unlike the criminal or judicial realm, the culprit is less to be punished than reformed.

Political framing links the harm with a condition to create the motivation to push through available solutions. In 1937, elixir sulfanilamide was the policy tragedy and bill S.1944 was the available solution.

In 1937, the Massengill Company in Bristol, Tennessee, was selling a drug called sulfanilamide. Sulfanilamide was one of the first true antibiotics in the family of sulfa drugs in that it specifically killed bacteria. It was used to treat venereal diseases in adults and streptococcal infections (strep throat) in children. The pills themselves were bitter tasting, so at the request of doctors and patients, the company developed an elixir for patients who

were unable to swallow the pills. The liquid needed to both dissolve the compound and have a more pleasant taste for children. The solvent chosen: diethylene glycol, a sweet-tasting liquid at room temperature known to cause damage to the blood, kidneys, nervous system and liver (21, 22).



**Figure 2.** The antibiotic sulfanilamide (above) was dissolved in diethylene glycol (below), a sweet tasting, but highly toxic solvent for distribution to adult and pediatric patients in 1937.

In October of 1937, 240 gallons of elixir sulfanilamide shipped to areas around the US. The first reports of death from the elixir came from the American Medical Association (AMA). On October 11, 1937, the president of the Tulsa, Oklahoma, County Medical Society, Dr. James Stevenson, sent a telegram to the AMA Chemical Laboratory stating that six people had died after taking the elixir. The AMA Chemical laboratory tested a sample of the elixir provided by the Massengill Company. Preliminary laboratory tests concluded that it was the solvent, diethylene glycol, and not sulfanilamide that had caused the deaths. The *Journal of the American Medical Association (JAMA)* issued a public warning on October 18, 1937 (23), and the story was reported by the press in the following days (24, 25).

The FDA learned of the deaths on October 14 and began the arduous recall process. One headline from the *New York Times* read (26)

#### Near End of Chase for Deadly Elixir

#### Government Agents Hope to Recover Today the Last of 700 Bottles

...Every agent of the United States Food and Drug Administration is scouring the country to recover the bottles, said Dr. Morris Fishbein, spokesman of the medical association. By some time tomorrow, according to J. O. Clarke of the Food and Drug Administration, it is hoped that all the outstanding shipments will be recovered.

—*New York Times*, October 25, 1937

When FDA inspectors reached the Massengill plant, they interviewed the chemists and found that no safety tests had been conducted. At the time, no toxicology testing was required. Under the 1906 law, which still applied in October 1937, the Massengill Company had only broken a mislabeling law. “Elixir” implied alcohol content and elixir sulfanilamide contained no alcohol. FDA Commissioner Walter Campbell was quick to point out that it was only the misbranding that had allowed the FDA to recall the elixir (24). Morris Fishbein, editor of JAMA, was also deeply troubled by the secrecy and absence of standardization from a reliable agency and supported strengthening of the FDA (19). In the four weeks that followed, the FDA was able to recall about 90 percent of the original shipment, but in the end there were 107 deaths (1).

In the aftermath of the tragedy, consumer advocate groups pushed for stronger legislation (27) and on November 16 and 17 of 1937, Royal Copeland (D-New York) and Virgil Chapman (D-Kentucky) successfully pressed for a USDA report, which was presented to Congress on November 26. The USDA report (the Wallace report) detailed the story from the failure of Massengill to test the elixir for toxicity to the technicality that allowed the FDA to enter a case and recall the elixir (28). Two of the most important points were that the elixir was tested for only flavor and not safety, and had the elixir been labeled “solution,” no charge of violating the law could have been brought.

The Wallace report was a strong narrative, but it was further strengthened by a copy of a letter written by Maise Nidiffer describing the agonizing death of her beautiful six-year-old daughter after taking the elixir. In her letter, Mrs. Nidiffer begged that similar pain not be caused again and attached a photograph of her child (19). At the end of the report were the following recommendations: Pre-market review and notification for new drugs, prohibition (or withdrawal) authority by the FDA, labeling regulations and compulsory disclosure of drug contents.

### The FD&C Act of 1938

President Franklin Roosevelt signed the FD&C Act into law on June 25, 1938 (29). The FD&C Act brought cosmetics and medical devices under FDA regulation, and required that drugs be labeled with directions for proper dosage and use. False therapeutic claims for drugs were clearly addressed and a separate law granted the Federal Trade Commission (FTC) authority over drug

advertising. Most importantly, the law required that all new drugs seek approval for safety and efficacy *before* sale (12). Approval required that a company show both efficacy and safety. The new law also corrected abuses in food packaging and created legally enforceable food standards. The law also authorized factory inspections and gave the FDA greater enforcement tools.

The FD&C Act of 1938 dramatically shaped drug development and sales in the US. After passage, companies needed scientists on staff to understand the drugs they were selling and the illness they were intended to treat. Companies were required to produce scientific tests for safety. It was the first US law to require the checking of drugs before they went to market. While initially intended to protect the public, the new law precipitated a shift that ultimately created the drug development industry we know today. After 1938, pharmaceutical companies began to invest large amounts of money to develop effective drugs to treat human illnesses and earn approval before selling their products. Companies adopted aggressive marketing practices to recover the cost of development and generate income before patents expired (1).

More new and effective drugs were invented between 1935 and 1955 than in all the previous years of human history. By the early 1950s doctors had many new and effective drugs in their arsenal to fight diseases. Medicine had become more specialized and new diseases had been identified. The study of clinical pharmacology was developing rapidly and newly hired FDA medical officers were increasingly trained in pharmacology (17).

In 1948, A. Bradford Hill, a British epidemiologist and biostatistician, and Harry Gold at the Cornell Medical School, began to organize formal criteria for drug testing. They introduced the concept of the double-blind study, in which neither the patient nor researcher knows who is receiving drug treatment. (It was well known at the time that doctors introduced bias, both knowingly and unknowingly, and gave drugs to healthier patients while weaker patients would receive the placebo.) In Hill and Gold’s protocols, patients were to be selected through formal criteria and randomly placed in treatment and control groups. Drug doses were to be administered according to a fixed schedule, and observations would be recorded at uniform intervals through objective diagnostic technologies (30). More sophisticated trial designs would follow. However, as of 1951, one estimate suggested that 45% of clinical trials still had no control group (31).

The 1938 Act required that new drugs be shown safe for use, but did not specify how this would be demonstrated. As the field of clinical pharmacology advanced, the FDA began to use the NDA as the instrument to enforce standards for efficacy. In 1955 and 1956, the FDA introduced new sections of the NDA requiring full descriptions of clinical results, including adverse effects and therapeutic results (32). Another unresolved issue from the 1938 law was the absence of clear protocols for clinical trials on humans. Some drug companies would circulate “investigational” samples of a drug to practicing physicians and ask for “reports” on safety and efficacy. FDA reviewers found themselves looking at testimonials rather than well-defined and controlled clinical studies (17).

In 1959, the US Senate began hearings to address pharmaceutical pricing. Initially the discussion, introduced by Senator Estes Kefauver (D-Tennessee), focused on profit margins and markups. The pharmaceutical industry, which had one of the highest markups, quickly pointed out that drugs costs covered more than just production expenses; research and development in the pharmaceutical industry were costly (17). The hearings soon turned to other topics, including the cost of clinical trials (17, 30). While Kefauver initially introduced legislation to address truth in labeling and marketing, the FDA contributed ideas to the legislation and pointed out weaknesses in the FD&C act. Ultimately the focus of bill, which had originally been intended (and drafted) to address pricing and truth in labeling, became about safety, efficacy and pre-market testing. Under the FD&C act, safety and effectiveness testing had not been clearly defined and companies could distribute a drug on an investigational basis *before* approval by the FDA.

Newspaper articles from the time reveal that the public was aware of the FDA’s policing functions to remove and regulate counterfeit or adulterated products (33) and public awareness of the drug approval process was also growing (34). In the spring of 1961, the Kefauver committee introduced bill S.1552, which was sent to committee and nearly completely gutted (17). A medical disaster was needed to move legislation forward. That disaster came when Morton Mintz published his article about the thalidomide tragedy in Europe and how the FDA had thwarted a similar disaster in the US. The headline read (35):

**“Heroine” of FDA Keeps Bad Drug Off of Market**

This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the

birth of hundreds or indeed thousands of armless and legless children.

—*Washington Post*, July 15, 1962



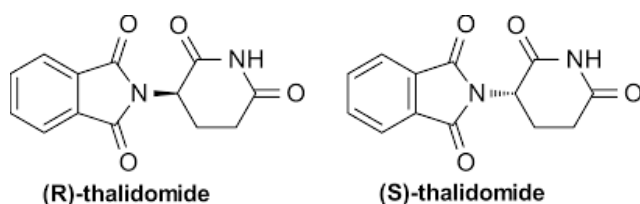
**Figure 3.** Frances Oldham Kelsey (36).

### Thalidomide

Frances Oldham Kelsey received her Ph.D. in 1938 in pharmacology from the University of Chicago and joined the faculty from 1938 to 1950. While at University of Chicago, she met her husband, Dr. Fremont Ellis Kelsey, and together they worked on a project to examine the effect of the drug quinine on rabbit embryos. They found that the liver of the mother rabbit contained an enzyme that could break down the drug, but the liver of the unborn rabbits did not contain the enzyme. The work highlighted the fact that some drugs may be safe for an adult, but dangerous to an embryo or fetus (37). Kelsey completed medical school at University of Chicago School of Medicine in 1950 and then served as an editorial associate at the American Medical Association. She taught pharmacology at the University of South Dakota from 1954 to 1957 and practiced medicine from 1957 to 1960. With a background in medicine and pharmacology, Kelsey was a perfect fit for the team of FDA reviewers and joined in 1960.

One of her first assignments at the FDA was to evaluate the drug thalidomide. Although she was pressured by the manufacturer, Richardson-Merrill, to quickly approve

the drug, which was already in widespread use in the rest of the world, Dr. Kelsey found the clinical reports more in the nature of testimonials rather than the results of well-designed and executed studies (38). There were no well-controlled animal or clinical studies, and the chronic toxicology data were incomplete (17). Kelsey also consulted the contemporary literature. She was further troubled by reports of peripheral neuropathy (loss of sensation in the extremities) as a result of thalidomide use (39), a side effect that the manufacturer had initially withheld in their application. She was concerned that the drug had not been adequately tested and cited the need for further study, effectively preventing a disaster in the US.



**Figure 4.** The enantiomers of thalidomide. The *R* enantiomer is a sedative and the *S* enantiomer is a teratogen. Early production methods produced a racemic mixture. However, once inside the human body, the enantiomers readily interconvert.

Thalidomide, sold from 1957 to 1961, was initially prescribed as a tranquilizer and painkiller. It was later found to be an effective antiemetic (anti-nausea) drug and subsequently prescribed to pregnant women for morning sickness. In 1957 it was sold over the counter in Germany, and by 1960, it was sold throughout Europe and in many other countries. The developer (West German pharmaceutical company, Chemie Grunenthal) claimed it was non-addictive, caused no hangover and was safe for pregnant women (38).

European physicians soon began reporting a disturbing phenomenon. A large number of women were giving birth to babies with severe birth defects. Some had abnormally short limbs and others had malformed internal organs or eye and ear defects. A German pediatrician, Widukind Lenz, began questioning his patients and found the 50 percent of the mothers who had given birth to children with birth defects had taken thalidomide in the first trimester of their pregnancy. In November of 1961, Lenz warned the manufacturer about his discovery of the dangers of thalidomide. Ten days later, German health authorities pulled the drug from the market in Germany (40).

More than 10,000 children in 46 countries were born with severe limb and other deformities as a consequence of their mother taking thalidomide, particularly during the first trimester of pregnancy. The number of children affected in the US was smaller than in Europe. However, the manufacturer had legally distributed thalidomide tablets to over a thousand doctors throughout the US on what was called an *investigational basis*. This was completely legal under the 1938 law. These doctors gave samples of thalidomide to nearly 20,000 patients, some of whom were pregnant (38).

Public awareness of the thalidomide disaster in Europe swiftly moved previously stalled legislation through Congress. In 1962, the Kefauver-Harris Amendments to the FD&C Act required each new NDA contain evidence from “adequate and well-controlled studies” demonstrating that a new drug was effective for its intended use and that the established benefits of the drug outweighed its known risks. Companies were required to present animal studies to the FDA *before* obtaining approval to test on humans. Clinical studies on humans would require informed consent from participants. The amendments further formalized manufacturing practices, required that adverse effects be reported and transferred regulation of advertising from the FTC to the FDA (41).

The 1962 Kefauver-Harris Amendments and the 1963 investigation drug regulations that followed marked a shift in investigation of new drugs in the US. One of the most dramatic changes was the pre-clinical trial process, in which drug developers were required to present evidence that a drug was safe enough to begin clinical trials. The Investigational New Drug (IND) submission and approval currently allows researchers to begin new drug trials on humans for a drug *under development*. In the IND application, companies submit preliminary animal toxicity data, manufacturing process, chemistry background and describe the initial clinical study protocol to be used. The data collected under an IND may later become part of the NDA for formal FDA approval (30).

### Off-Label Use and the Comeback of Thalidomide

As thalidomide was being withdrawn from the markets in Europe in the 1960s, doctors at Hebrew University were prescribing it as a sedative for patients with leprosy. They noticed that the drug also alleviated erythema nodosum leprosum (ENL), a type of lesion and nerve deterioration common in leprosy patients.

Later at Rockefeller University in New York, researchers discovered that the drug inhibited a protein called tumor necrosis factor alpha (42), a common cause of inflammation in rheumatoid arthritis, tuberculosis, and Crohn's disease.

In another area of biochemistry, researchers were searching for molecules that would prevent angiogenesis (new blood vessel formation) as a possible treatment for cancer. It was well known that tumors will recruit a new blood supply to feed their rapid growth. Surgeons have long observed that upon removing a tumor, the tumor itself is replete with blood vessels. The idea behind this project was to prevent angiogenesis and thereby starve a tumor. While not an absolute cure, it was a treatment. Thalidomide inhibited angiogenesis for tumor cells in rodents (43). Today there are numerous papers on thalidomide's anti-inflammatory and anti-myeloma activity in adults (44). This discovery explained how thalidomide caused birth defects by targeting blood vessels formation in an embryo.

In 1996, 34 years after the passage of the Kefauver-Harris Amendments, the Celgene Corporation applied for an NDA for thalidomide. In spite of promising results in the area of HIV and cancer, the application was filed for the ENL condition in leprosy (pretty rare in the US), but this is where the company had its strongest data. An advisory committee that included a thalidomide victim, voted to approve thalidomide and a year later the FDA made it official, with the condition of a strict regimen for controlling access to the drug and preventing birth defects (45, 46). The FDA would be more directly involved in selecting and warning patients, an approach used with the drug Accutane that can also cause severe birth defects (47). By 2004, nearly 92 percent of the thalidomide prescriptions were for a type of cancer called multiple myeloma, an unofficial or off-label use. Thalidomide was officially approved for cancer treatment in 2006 (48).

In 1997, Congress passed the Food and Drug Administration Modernization Act to further clarify the role of the FDA with the development of new biotechnologies and treatments from these emerging areas (49). It also formally addressed criticism from activists representing patients with terminal illnesses and the lag time for drug approval. The new law accelerates the review of devices, provides guidelines to regulate advertising of unapproved uses of previously approved drugs and regulates health claims for foods.

The FD&C Act of 1938 and the Kefauver-Harris amendments in 1962 advanced the powers of the FDA

and prompted the evolution of the modern pharmaceutical industry in the US. The FD&C act of 1938 opened the door for effective federal food and drug regulation and marked the ending of the quack medicine industry. The Kefauver-Harris amendments in 1962 further strengthened the FD&C Act and clarified regulations for drug testing and clinical trials. Both pieces of legislation were the product of mounting consumer activism, political pressure and were ultimately pushed to passage by high profile tragedies.

**Table 1.** Some of the landmark Congressional FDA legislation.

- The Biologics Control Act (1902): Ensured purity and safety of serums, vaccines and similar products used to prevent or treat diseases in humans.
- The Pure Food and Drugs Act (1906): Provided for federal inspection of meat and forbade the manufacture, sale or transportation of adulterated food products and poisonous patent medicines.
- The Federal Food, Drug, and Cosmetic Act (1938): Following the elixir sulfanilamide tragedy, the FD&C Act completely overhauled the public health system. Among other provisions, the law authorized the FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections.
- The Kefauver-Harris Amendments (1962): Following the disfiguring birth defects linked to the drug thalidomide, this amendment strengthened the rules for drug safety, required informed consent during clinical studies and required manufacturers to prove their drugs' effectiveness.
- The Medical Device Amendments (1976): Followed a US Senate finding that faulty medical devices had caused 10,000 injuries, including 731 deaths. The law applied safety and effectiveness safeguards to new devices.
- Food and Drug Administration Modernization Act (1997): This law accelerated the review of devices, provided guidelines to regulate advertising of unapproved uses of previously approved drugs and regulated health claims for foods.

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### About the Author

Jessica Epstein is a Professor of Chemistry and Department Chair at Saint Peter's University. She received a B.S. in Chemistry from the Georgia Institute of Technology and a Ph.D. in Biochemistry from the University of Maryland. She completed a post-doctoral fellowship in the Department of Cell and Molecular Biology at Harvard University.

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The International Union of Pure and Applied Chemistry (IUPAC) will celebrate its 100<sup>th</sup> anniversary in 2019. It will hold its 50<sup>th</sup> General Assembly and 47<sup>th</sup> World Chemistry Congress in Paris, July 5-12, 2019 ([iupac.org/100/](http://iupac.org/100/)).