Promoting Safe and Effective Drugs for 100 Years

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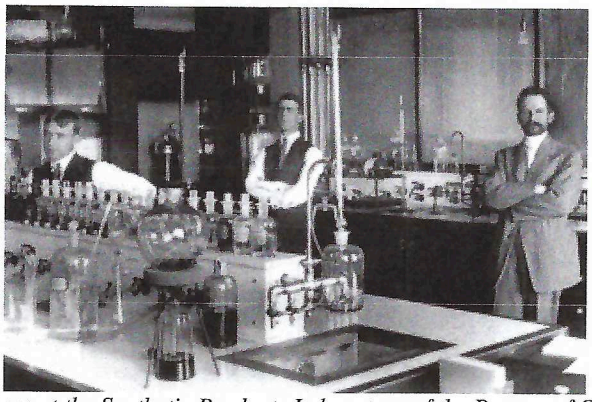

Researchers at the Synthetic Products Laboratory of the Bureau of Chemistry include (left to right) Rex Shiveley, L.B. Mears, and W.O. Emery. In 1907, this laboratory's major research project involved assessing drug ingredients.

At the turn of the 20th century, there were no federal regulations to protect the public from dangerous drugs. "It was a menacing marketplace filled with products such as William Radam's Microbe Killer and Benjamin Bye's Soothing Balmy Oils to cure cancer," says John Swann, Ph.D., a historian at the Food and Drug Administration in Rockville, Md. "Products like these were, at minimum, useless remedies that picked the pocket of the user, but they could also be downright harmful."

Today, the drug review process in the United States is recognized worldwide as the gold standard. Drugs must undergo a rigorous evaluation of safety, quality, and effectiveness before they can be sold.

I think the FDA's biggest contribution to health has been through its progress in evidence-based medicine," says Steven Galson, M.D., who has served as director of the FDA's Center for Drug Evaluation and Research (CDER) since July 2005. "Before the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, controlled trials were still developing, and many marketed drugs were ineffective for their labeled uses. Now, the standard for evidence is the well-controlled study, and the FDA's implementation of the 1962 amendments contributed greatly to that."

Controlled trials also contribute to effective safety evaluation, and the FDA's review of all pre-marketing safety data is far more sophisticated than ever before, Galson says. Drugs undergo a complete evaluation of their metabolism, their interactions with other drugs, and potential differences in safety and effectiveness for people of different genders, ages, and races.

The CDER serves as the consumer watchdog for the roughly 11,000 drugs on the market. Drugs include prescription and over-the-counter (OTC) medicine, as well as fluoride toothpaste, antiperspirants, dandruff shampoos, and sunscreens. Along with approving beneficial drugs for marketing, the CDER regulates the manufacturing, labeling, and advertising of prescription drugs.

An important step toward organizing federal research into drugs, and eventually their regulation, began in 1902. Harvey W. Wiley, M.D., a chemist with the U.S. Department of Agriculture, announced the formation of a Drug Laboratory during the annual meeting of the American Pharmaceutical Association. Lyman Frederic Kebler, M.D., a chemist from the Philadelphia firm Smith Kline and French, served as director of the laboratory from 1903 to 1923. At first, Kebler was a one-man operation. Now the CDER, with more than 2,200 employees, is the largest of the FDA's five product centers.

"Over the years, CDER has reorganized several times to become more efficient and respond to scientific and legislative mandate," Galson says. "Our mission continues to focus on ensuring that the benefits of drugs outweigh all known risks. With every milestone, we've put patients first."

The First Federal Drug Law

The original Pure Food and Drugs Act was passed by Congress in 1906 and signed by President Theodore Roosevelt. The law, which prohibited misbranded and adulterated foods, drinks, and drugs in interstate commerce, was enforced by the Bureau of Chemistry in the Department of Agriculture. The bureau became the Food and Drug Administration in 1930.

There was no requirement, however, that any information be submitted to the FDA before marketing, and the law required only that drugs meet standards of strength and purity. The burden of proof was on the government to show that a drug's labeling was false and misleading before it could be taken off the market.

Swann says that one of the first major challenges to drug regulation came in 1910 when the government seized a large quantity of a worthless 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 Drugs Act.

Congress enacted the Sherley Amendment in 1912 to overcome the ruling in U.S. v. Johnson. This amendment prohibited labeling medicines with false therapeutic claims intended to defraud the purchaser. But the amendment wasn't ideal. The government still had to prove that there was intent to defraud.

"To establish fraud, the bureau had to show that the manufacturer knew the product was worthless, and this proved difficult in many cases," Swann says. For example, Lee Barlett, a former shirt salesman from Pittsburgh, promoted a medicine called Banbar as being effective for diabetes. Banbar was an extract of horsetail weed. The government took Barlett to court for

selling a misbranded drug and even showed the death certificates of people with diabetes who had taken Banbar. But the jury ruled in Barlett's favor.

The Food, Drug, and Cosmetic Act of 1938

A bill was introduced in the U.S. Senate in 1933 to overhaul the 1906 drug law. But congressional action stalled. Revised legislation wasn't passed until 107 people died from a poisonous ingredient in Elixir Sulfanilamide. The S.E. Massengill Co. of Bristol, Tenn., had been marketing the product, which was the chemical relative of antifreeze now used in automobiles.

"Many of those who died were children, including a 6-year-old girl from Tulsa," Swann says. The girl's mother, Marie Nidiffer, wrote to President Franklin Roosevelt about her grief.

Congress passed the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 with new provisions. President Roosevelt signed it into law on June 25, 1938. For the first time, manufacturers were required to show that a drug was safe before it could be marketed.

Manufacturers had to submit an application to the FDA before marketing a drug. If the FDA didn't act on the application in a certain time period, the application automatically became approved.

The 1938 act also eliminated the Sherley Amendment, which called for adequate labeling for safe use, set safe tolerances for unavoidable poisonous substances, and authorized factory inspections. In 1951, the Durham-Humphrey Amendment to the act was passed. This amendment created requirements that certain drugs be labeled for sale by prescription only.

The Kefauver-Harris Drug Amendments

In 1962, news reports about how FDA Medical Officer Frances O. Kelsey, M.D., Ph.D., had kept the drug thalidomide off the U.S. market aroused public interest in drug regulation. Thalidomide had been marketed as a sleeping pill by the German firm Chemie Grunenthal, and was associated with the birth of thousands of malformed babies in Western Europe.

"In the years before 1962, Senator Estes Kefauver had held hearings on drug costs, the sorry state of science supporting drug effectiveness, and the fantastic claims made in labeling and advertising," Temple says. "Well-known clinical pharmacologists explained the difference between well-controlled studies and the typical drug study. With the FD&C Act 'in play' because of thalidomide, Congress had the opportunity to make major changes."

In October 1962, Congress passed the Kefauver-Harris Drug Amendments to the Federal FD&C Act. Before marketing a drug, firms now had to prove not only safety, but also provide substantial evidence of effectiveness for the product's intended use. Temple says, "That evidence had to consist of adequate and well-controlled studies, a revolutionary requirement."

"Also critically, the 1962 amendments required that the FDA specifically approve the marketing application before the drug could be marketed, another major change." The Kefauver-Harris

Drug Amendments also asked the Secretary to establish rules of investigation of new drugs, including a requirement for the informed consent of study subjects. The amendments also formalized good manufacturing practices, required that adverse events be reported, and transferred the regulation of prescription drug advertising from the Federal Trade Commission to the FDA.

Stricter Labeling Requirements

In 1966, the Fair Packaging and Labeling Act required all consumer products in interstate commerce to be honestly and informatively labeled, with the FDA enforcing provisions on foods, drugs, cosmetics, and medical devices. In 1970, the FDA required the first patient package insert; oral contraceptives had to contain information about specific benefits and risks in language that patients can understand. Emphasis on OTC labeling came in 1972, when the FDA began reviewing OTC drugs for safety and effectiveness.

In 1981, formal standards for the Protection of Human Subjects and Institutional Review Boards (IRBs) were strengthened. The IRBs are panels of scientists and non-scientists in hospitals and research institutions who ensure the safety and well-being of human subjects involved in research.

The standards clarified FDA requirements for informed consent and provided protection of the rights and welfare of human subjects involved in research within the FDA's jurisdiction.

Drug sponsors must show the FDA results of preclinical testing they've done in laboratory animals and what they propose to do for human testing before they can begin. This information is presented in an investigational new drug application (IND). Clinical trials--drug studies in humans--can begin only after an IND is reviewed by the FDA and an IRB.

Anti-Tampering Regulations

After seven people in Chicago died from swallowing Tylenol capsules laced with cyanide, the FDA issued Tamper-Resistant Packaging Requirements in 1982. The Federal Anti-Tampering Act, passed in 1983, makes it a crime to tamper with packaged consumer products.

According to FDA regulations, a tamper-resistant package has one or more indicators or barriers to entry that, if breached or missing, can reasonably be expected to give consumers visible evidence that tampering has occurred.

The Orphan Drug Act

"Orphans" are drugs and other products used to treat rare diseases. People affected by rare diseases created a groundswell of support for legislation, and the Orphan Drug Act (ODA) was passed in 1983. It allowed the FDA to encourage research and development of drugs needed to treat rare diseases. Before this time, people with rare diseases were denied access to effective medication because manufacturers could rarely make a profit marketing drugs to such a small group.

The ODA created financial incentives, including tax credits for the costs of clinical research and seven years of marketing exclusivity for the first sponsor of an orphan product who receives FDA approval for a particular indication.

Examples of rare diseases that can now be treated with orphan medications include sickle cell anemia, cystic fibrosis, and T-cell lymphoma.

Encouraging Generic Drugs

The Drug Price Competition and Patent Term Restoration Act of 1984 expanded the number of drugs for which an abbreviated new drug application (ANDA) could be submitted. The ANDAs make it less costly and time consuming for generics, which are often sold at lower prices than brand-name drugs, to reach the market.

Generic drug companies don't have to repeat the expensive clinical trials that brand companies have already conducted to show safety and effectiveness. But they must perform tests and show the FDA that their drugs are equivalent to the brand name in terms of therapeutic effect. These companies must show that an equivalent amount of the active ingredient of the generic drug enters the bloodstream over the same length of time and to the same extent as it does in the brand-name drug.

"Because the cost of medicine is a concern to so many Americans, expanding access to generic drugs will continue to be a critical area for the agency," Galson says.

The 1984 act encourages production of generics while protecting rights of brand-name manufacturers. The law builds in certain protections for the original drug developer in terms of patents and market exclusivities to encourage further drug development, but it also allows sponsors of identical generic products to apply for their approval by the FDA without repeating the original developer's clinical trials. In certain instances, the law also rewards a period of exclusive marketing for the first generic version of a brand-name drug to challenge a patent, thereby encouraging generic firms to challenge innovator patents. Not all medicines are eligible for generic competition because of innovator patents or exclusivities.

The CDER's Office of Generic Drugs was established in 1989.

Drugs for Life-Threatening Illnesses

Several programs have been initiated to help people with life-threatening illnesses get quicker access to drugs. The "treatment use of investigational drugs" (IND), proposed in 1982 and allowed in a final regulation in 1987, allows promising investigational drugs to be given to people with life-threatening diseases for which there is no alternative while the data to support marketing are being collected.

Another example of improving access to treatment is "accelerated approval," which was formalized in 1992. This type of drug approval is based on an encouraging effect such as tumor

shrinkage, before there is actual evidence of improved survival or other clinical benefit, Galson says. "Accelerated approval has allowed us to make significant strides in improving treatment options for people with cancer and other serious diseases." The FDA approves a drug under accelerated approval on the condition that the drug manufacturer verify the actual clinical benefit.

The Prescription Drug User Fee Act

"For a long time, people lauded the quality of the CDER drug review process, but criticized it for being too slow," says Janet Woodcock, M.D., former CDER director and deputy commissioner for operations at the FDA. "The FDA began to address the issue with the establishment of user fees." The Prescription Drug User Fee Act (PDUFA) was passed in 1992, and mandated that drug companies pay user fees so the FDA could add more resources and speed up drug review times, without compromising standards.

"In exchange for the additional resources, the FDA makes a commitment to meet certain goals for review times," Woodcock says. For example, by 2002, the FDA's reviews of all marketing applications for new drugs were to be completed in 10 months. The PDUFA allowed the agency to have a 60 percent increase in staff assigned to review new drug applications. Woodcock says, "CDER has exceeded almost all of the goals set by PDUFA."

In 1997, the PDUFA was renewed under the Food and Drug Administration Modernization Act and then renewed again in 2002 for five more years.

The Food and Drug Modernization Act of 1997

In addition to reauthorizing the PDUFA, the Food and Drug Modernization Act (FDAMA) supported accelerated approval and gave an extra period (six months) of marketing exclusivity to manufacturers that carried out studies in children.

This legislation affirmed the CDER's public health protection role, calling for the FDA to continue promoting the public health by efficiently reviewing drugs and to join with representatives of other countries to harmonize regulatory requirements.

Improving Post-Marketing Drug Safety

Because it's not possible to predict all of a drug's effects during clinical trials, monitoring safety issues after drugs get on the market is critical. "The role of our post-marketing safety system is to detect serious unexpected adverse events and take definitive action when needed," Galson says.

In 1993, the FDA launched MedWatch, a voluntary system that makes it easier for physicians and consumers to report adverse events. In addition to relying on MedWatch, the CDER evaluates required reports from drug companies.

Usually, when important new risks are uncovered, the risks are added to the drug's labeling and the public is informed of the new information through letters, public health advisories, and other

education. In some cases, the use of the drug must be substantially limited. And in rare cases, the drug needs to be withdrawn from the market.

"Drug safety will always be a high priority for the agency," Galson says. "On an ongoing basis, we look for ways to improve how we communicate drug risks to the public."

In 2005, the FDA formed the Drug Safety Oversight Board to advise the CDER. Board members include FDA staff and representatives from the National Institutes of Health and the Veterans Administration.

Fighting Terrorism

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 was passed in the aftermath of the terrorist events of Sept. 11, 2001. The law aims to improve the country's ability to respond to public health emergencies. Provisions include a requirement that the FDA issue regulations to enhance controls over imported and domestically produced commodities it regulates.

The Project BioShield Act of 2004 authorized the FDA to speed up its review procedures to allow for the rapid distribution of treatments as countermeasures to chemical, biological, and nuclear agents that may be used in a terrorist attack against the United States. "This emergency use authorization is an example of how the FDA works to defend the nation in times of need," Galson says.

What's Ahead?

All of these major issues in the history of drug regulation will continue to be important, Galson says. "I think our product quality initiative will fundamentally change the FDA's role in drug manufacturing oversight." Announced in 2002, the "Product Quality for the 21st Century Initiative" focuses on the greatest risks to public health in manufacturing procedures and ensures that quality standards don't impede innovation.

The CDER also will help streamline the path for developing new drugs. In 2004, the FDA published "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." This document examines how the FDA can help make medical breakthroughs available to those in need as quickly as possible.
"I think we'll also see an increase in personalized medicine. We know that patients can respond differently to medicine. More genetic information will be considered in the drug development process in the coming years," Galson says. "The FDA considers personalized medicine a major opportunity on the critical path to new medical products."

"The FDA also wants to be sure the public understands and can observe critical points of the process that brings drugs to the marketplace," Galson says. "Advisory committee meetings are an important way for people to observe the FDA's decision-making process. We want to make our drug review, approval, and monitoring programs as transparent as possible. Outside advisors also contribute to the quality of these programs."

"Our work affects millions of Americans, and CDER's staff and leadership remain committed to patients' needs."

Expanding Demographics in Clinical Trials

In the 1980s and 1990s, several FDA guidance's and rules drew attention to the need to include representative populations in clinical trials. The inclusion of such populations has helped experts analyze results for possible differences in drug response among demographic subsets. Here are some key changes that have helped expand demographic evaluation in drug research:

- In 1989, the FDA issued guidelines asking manufacturers to determine whether a drug is likely to have significant use in older people, and to include older patients in clinical studies.
- In 1993, the FDA issued the Gender Guideline, which called for assessments of medication responses in both genders. In the Federal Register notice announcing the guideline, the FDA also revoked a 1977 guideline that excluded women of childbearing potential from early clinical studies.
- In 1998, the FDA required that a marketing application analyze data on safety and effectiveness by age, gender, and race. This is known as the Demographic Rule.
- In 1998, the FDA promulgated the Pediatric Rule, a regulation that required manufacturers of selected drugs to conduct studies to assess their safety and efficacy in children. A federal district court later overturned the pediatric rule. Tommy G. Thompson, former Secretary of the U.S. Department of Health and Human Services, responded by announcing that his department would push for rapid passage of legislation that would give the FDA authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on drugs.
- In 2002, the Best Pharmaceuticals for Children Act was passed to improve the safety and effectiveness of 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 if a manufacturer fulfills its commitment to carry out studies of the effects of drugs when taken by children. The six months of exclusivity applies to all approved indications (adult or pediatric).
- In 2003, the FDA was given clear authority under the Pediatric Research Equity Act to require drug sponsors to conduct clinical research into pediatric applications for new drugs.