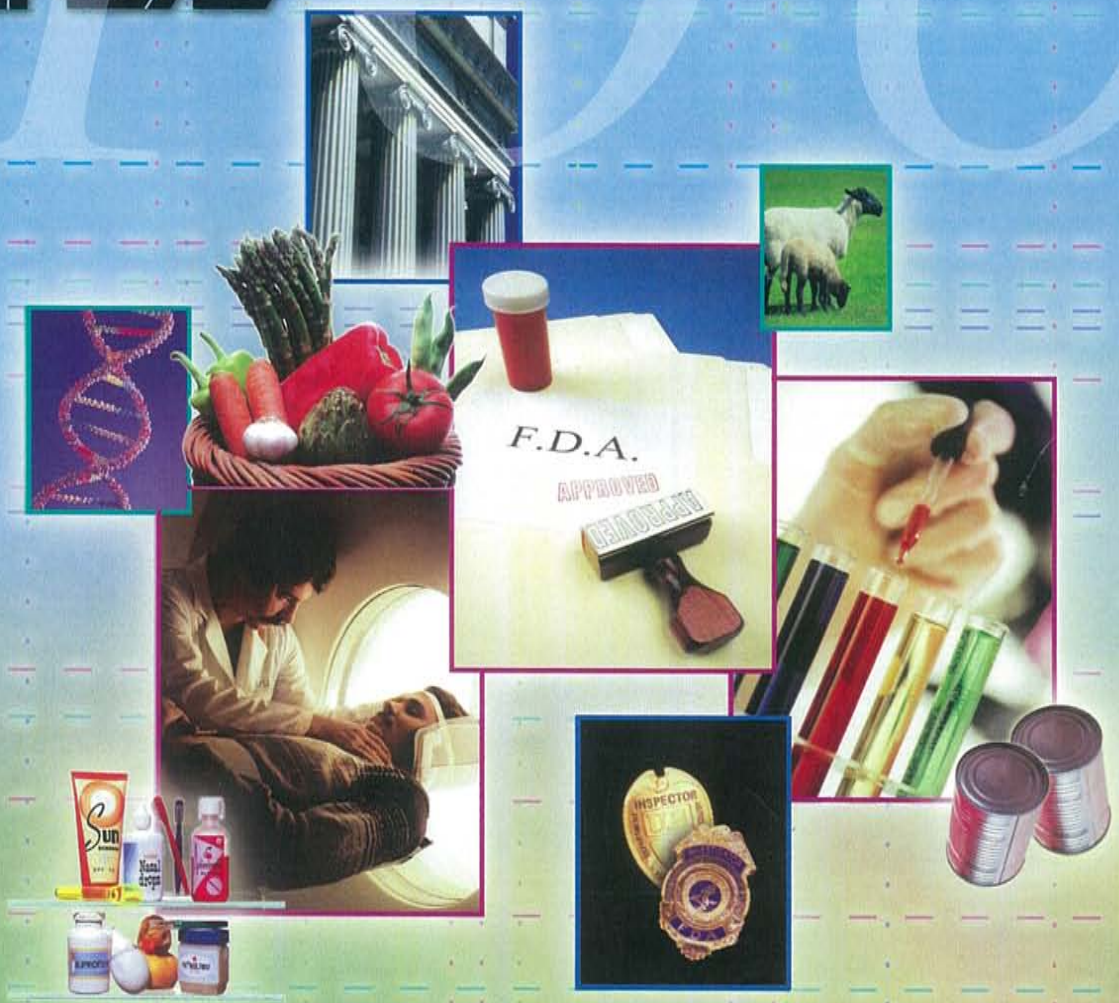
100

FOOD & DRUG ADMINISTRATION

FDA



A CENTURY OF CONSUMER PROTECTION

WAYNE L. PINES
EDITOR

FDLI

FDA in the World Community

Linda Horton

It is fair to say that the Food and Drug Administration in the United States has won tremendous consumer confidence which is the envy of the world.
—John Bruton

THE YEAR WAS 1997, the speaker the Prime Minister, the audience the Irish parliament when John Bruton reported on a meeting with FDA officials during a St. Patrick's Day trek to Washington. Reeling through the "mad cow crisis," government leaders in many countries were seeking FDA guidance about how to strengthen food safety and consumer confidence.

How did FDA become the international benchmark for science-based regulation, public health-oriented decision-making, transparency, industry responsibility, stakeholder involvement, enforcement, and rule of law? The Irish leader's consultation was not the first time officials abroad had examined the FDA model. Just as FDA in its first century came to be recognized in the United States as the premier domestic consumer protection agency, FDA enjoyed high stature internationally. From the beginning, international influences played a key role in shaping U.S. food and drug law and the agency itself.

Perhaps the most important international influence on U.S. food and drug law has been scientific collaboration. In the last quarter of the nineteenth century, our nation was still a scientific backwater. In a quest for greater knowledge, in 1878, Dr. Harvey Wiley embarked on a trip to Europe to study at leading universities. In his 1930 autobiography, Wiley recounted the influence of this trip on his decision to abandon plans to practice medicine and instead pursue efforts to detect and deter food adulteration. Wiley's studies in the laboratories of Vienna, Berlin, Bonn, Heidelberg, Leipzig, and London expanded his knowledge of analytical chemistry and gave him a network with other pioneers in the field.

After Wiley was appointed Chief Chemist of the Department of Agriculture (USDA) in 1883, he continued these international collaborations, returning to Europe in 1885 to collaborate with French, German, and British scientists and to observe Spanish sugar producers. While President

of the American Chemical Society, Wiley organized the first World Congress of Chemists, held in 1892 in Chicago. In 1902 he sought advice from officials of the Imperial Board of Health in Berlin about how to conduct scientific experiments to ascertain the safety of food additives, a consultation that might have influenced his formation of the famous Poison Squad. A year after passage of the 1906 Pure Food and Drugs Act, he assisted the French government in modifying its food law. Two years later he attended an international applied chemistry congress where he addressed the Prince of Wales concerning the benefits of international cooperation.

A second early international influence on U.S. food and drug law involved legislative concepts. Not surprisingly, given our history, British law was a principal source of inspiration. The bedrock legal concepts of "adulteration" and "misbranding" had first appeared in late nineteenth century British legislation and in due course found their way into draft laws in Canada and the United States. In 1881 an Englishman, Professor G. W. Wigner, won $1,000 in a contest sponsored by a U.S. trade association for the best draft food law. Wigner's draft covered drugs as well as food, an innovation that increased interest in a federal statute that addressed unsafe and fraudulent patent medicines, as well as food. Wiley said this "proposed law had a deep effect on subsequent legislation on the subject."

A third international influence on U.S. food and drug law was concern about the safety of imports, an issue that has carried over into the twenty-first century with enactment of laws such as the 2002 anti-bioterrorism law, the first major strengthening since 1938 of FDA's food authority. The earliest federal food and drug laws—the Drug Importation Act of 1848, the Tea Importation Acts of 1883 and 1897, the Food and Drug Importation Act of 1890, and the Food Importation Act of 1899—applied only to imports. Domestic producers were regulated by states or not at all.

The various import control laws stemmed from the view of some foreign exporters who saw the United States as a dumping ground for inferior products, deemed "good enough for America." An 1848 Congressional Committee Report said that America had "become the grand mart and receptacle of all the refuse merchandise ... not only from European

The Most Important...

The FDA was the first agency in the world to attempt broad scientific review of foods and drugs, and its standards have remained the highest. It is the most known, watched, and imitated of regulatory bodies. Because of its influence outside the United States, it has also been described as the most important regulatory agency in the world.

—**Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (2003).**

warehouses but from the whole eastern world." Vast quantities of filthy, sub-potent, and fraudulent pharmaceutical ingredients had overwhelmed U.S. port authorities and undermined the health of soldiers fighting in the Mexican War. A year after the Drug Importation Act was passed, more than 90,000 pounds of inferior drugs were turned back from the Port of New York. Eventually, however, the 1848 drug import law was judged a complete failure. Problems were rampant corruption and statutory neglect of four key needs: an effective enforcement process, a cadre of honest

Inspector John Earnshaw inspected imported food products at the port of Baltimore, circa 1912.

and dedicated scientific and enforcement officials, meaningful standards for pharmaceutical acceptability, and coverage of all drugs, including domestic as well as imported products. The creation of the agency now known as FDA and enactment of the Pure Food and Drugs Act of 1906 began to address these needs.

The Drug Importation Act placed several European pharmacopoeias on the same plane as the U.S. Pharmacopeia (USP), founded in 1820. From 1848 until 1906, the definition of "drug" in federal law included not only products referenced in the USP but also ones listed in the pharmacopoeias of Edinburgh, London, France, and Germany. The 1906 Pure Food and Drugs Act referred only to the USP and the National Formulary. Thus, the provisions in the 1997 FDA Modernization Act (FDAMA) for harmonization of regulatory requirements and mutual recognition arrangements with Europeans had early statutory antecedents going back a century and a half.

The 1899 law that empowered the Bureau of Chemistry to stop imports of adulterated or misbranded foods and drugs

European Leader on FDA and ICH

Fernand Sauer, the European Commission's public health director-general and one of the chief architects of the European drug regulatory system, has "always had a great respect for the capacity of the FDA to mobilize scientific debate." Mr. Sauer's dealings with FDA began in the late 1980s when the commission and FDA initiated bilateral meetings. At the time, Mr. Sauer was in charge of the commission's pharmaceuticals unit, and he met with FDA to figure out whether the European Community was about to become a "fortress Europe" that would saddle producers with Euro-specific requirements as extensive as, yet different from, those of FDA.

From Mr. Sauer's early discussions with Japanese leaders, with FDA officials Elaine Esber, Stuart Nightingale, Carl Peck, and Roger Williams, and with industry representatives, there arose a tripartite commitment to work together toward uniform global standards for drug testing. The International Conference for the Harmonization of the Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) was formally inaugurated in 1990.

According to Mr. Sauer, ICH achieved a "spectacular success, given the investment put in, by the end of the 1990s." He believes that "international harmonization should be a by-product of what [regulatory officials] do anyway, not a distinctive activity ... [or an] international diplomatic activity." Furthermore, "since the WHO didn't exercise this function, we offered it to WHO as a contribution of the three main regions where pharmaceutical research is done." The biennial conference to announce progress was "deliberately a public event, with 1,200 delegates to the 1990 conference" and multiples of this number at later ICH biennial conferences.

Industry was at the ICH table from the beginning "to get the best experts" and avoid the "danger that regulators would undertake pet projects that aren't relevant" to product development, according to Mr. Sauer, However, the public interest is paramount, he said, as government representatives from FDA, European authorities, and the Japanese health ministry have controlled the agenda and have taken responsibility for adopting ICH guidelines into their own regulatory systems.

Mr. Sauer said most FDA participants enjoyed their ICH assignment—it added interest and an additional purpose to their work. Also, he believes that the agency gave a lot of recognition to FDA experts who contributed to ICH. Originally they had feared that harmonization meant lowering standards, while the

led it to establish the first district offices and field laboratories to police food and drug imports. Experience gained under this law equipped the bureau for its duties under the 1906 Act. Also in the 1890s, a sister unit in the USDA, the Bureau of Animal Industries—predecessor to today's Food Safety Inspection Service—was authorized to inspect meat imports and exports. Beginning in 1879, the notoriously poor quality of U.S. meat, often infected with trichinae, led other countries to ban U.S. meat. The early export and import control laws must not have been working, because Upton Sinclair's famous account of disgusting conditions in the U.S. meat-packing industry helped propel into law both the languishing Pure Food and Drugs Act and a meat inspection law covering products for U.S. consumption as well as exports. Both laws were signed on June 30, 1906. The debate leading up to passage of the 1906 Food and Drugs Act included heated arguments—heard again when Congress debated export laws in 1976, 1986, and 1996—as to whether U.S. exports should be required to meet U.S. standards. The 1906 decision was

drug industry feared the opposite. However, the rigorous but sensible ICH output, at a high level of scientific quality, ultimately won over most skeptics, he said.

For Europe, he said, "we had to adjust the regulatory guidance anyway," and ICH "provided the chance to get the best advice from outside" on how this might best be done. "Since each member state had to change its ways, why not do it in harmony with the U.S. and Japan?" Mr. Sauer also credits ICH—and the opportunity it afforded to work with FDA on scientific matters—with helping to pave the way for the intensified technical cooperation effort demanded of European member country experts when the European Medicines Agency (EMEA) began operations in 1995. Despite cooperation since 1975 among European Community experts through a group known as the Committee on Proprietary Medicinal Products, "in the 1986–93 time period, we were not sure we could actually create the EMEA," and ICH helped prove what could be done, he said.

Asked whether FDA and the EMEA are competitors, Sauer said, "The competition was always in a friendly way, not confrontational, and not with the view that anyone had failed." With ICH, the EMEA, and now the new Japanese Pharmaceutical and Medical Devices Agency, FDA is no longer the sole reference point, although he hastened to add that "FDA is still the benchmark."

Fernand Sauer perhaps is a modern European Harvey Washington Wiley. In addition to the key role he played in ICH's birth, Mr. Sauer was chief architect of the EMEA and served as its first Executive Director from 1994 to 2000. He then moved to head the European Community's burgeoning public health responsibilities and was responsible for establishment of the European Centre for Disease Prevention and Control (ECDC). Quite naturally, the ECDC works closely with its larger and older U.S. counterpart.

Looking back on his involvement with FDA, Mr. Sauer said, "What I recollect best are the people in FDA, people who were ready to do things. We always found solutions, and there was always a lot of good will."

Interviewed by Linda Horton in Brussels, May 17, 2005

that compliance with receiving country requirements would suffice.

In later years, international influences seem to have become less important for a time than they had been during Wiley's era and again at the end of the twentieth century. FDA annual reports recount more or less constant frustration with non-compliant imports during the era in which several of the first international inspections occurred. In 1910 FDA sent an investigator to learn why so many Turkish figs were contaminated with insects and worms. This episode and the efforts that followed may have been the Bureau of Chemistry's first technical assistance project, carried out in parallel with efforts to raise standards in California's fledgling fig industry.

International issues played no discernible role in the enactment of the Federal Food, Drug, and Cosmetic Act of 1938. However, like other U.S. institutions, FDA was

When the Call of Duty Demands Too Much

I will never forget the morning of Thursday, January 11, 1990, the day that marks the only time FDA employees have lost their lives in the line of duty. Arvin Shroff, Deputy Director of the Office of Enforcement, Office of Regulatory Affairs, walked into my office and told me that the plane carrying my colleague and friend, Jack Harty, and another colleague, Pat Pouzar, was missing. I was the Deputy Director of the International Affairs Staff at the time and Jack was the Director. I immediately wanted to know everything about the situation, and I informed the staff. Needless to say, not much work got done the rest of the day.

During the previous year, an anonymous call to the agency reported that grapes contaminated with cyanide were being shipped from Chile to the United States. After FDA laboratories detected cyanide in grapes at the port in Philadelphia, FDA acted quickly to protect the public health, detaining shipments of all fruit from Chile. Of course, there were tremendous ramifications for the fruit industry in Chile, as consumers became wary of fruit from Chile. The Chilean government responded by trying to ensure that their product was indeed safe and sought FDA's blessing of the process and the security mechanisms they had put in place.

During 1989, John F. Harty, Jr., Director of the International Affairs Staff, Office of Health Affairs, had been an integral part of the negotiations, which culminated in a formal memorandum of understanding between FDA and the Agriculture and Livestock Service of the Ministry of Agriculture of Chile. The government of Chile invited FDA to send a team to Chile to review the procedures it had put in place to ensure the safety of fruit exported to the United States. In response, Jack Harty, FDA's resident diplomat and former investigator, and Pat Pouzar, an accomplished investigator and Acting Director of the Nashville District Office, scheduled a visit.

During the trip to Chile, the FDA team visited several sites that processed fruit for export. To accomplish their mission in an efficient manner, they traveled to at least one site on a small aircraft. Tragically, during their return flight to Santiago, the plane crashed into a mountainside. During the hours and days that passed from the time we learned that the plane was missing until we got word on Saturday night that the wreckage had been found, many dedicated colleagues and friends worked tirelessly to bring the necessary resources to bear on the situation. The Director of the Office of International Health in the Department of Health and Human Services, Linda Vogel, made her office available as a command center for communications with anyone we could think of, including the Secretary of Defense, to make search and rescue aircraft available.

I cannot fully describe the feelings among us in Linda's office that night as we eagerly awaited a call from the Defense Department. Instead, the call came from the State Department to say that the crashed plane had been found and that there were no survivors.

affected by wars. Wartime considerations reportedly influenced the 1940 decision of President Roosevelt to leave the meat inspection program with USDA when he transferred FDA to the new Federal Security Agency, predecessor to today's Department of Health and Human Services. Beef industry interests had argued that, with the war already underway, it was no time to change regulation of a key export commodity needed for the allied effort. On the drug side, supplies of many products were interrupted at the very time demand increased, and the head of the Pharmaceutical Manufacturers Association (now PhRMA) once said that World War II forced the maturation of the U.S. industry. The military's need for reliable supplies of penicillin led to the passage of special legislation to establish a product testing and certification program for this product and later for others.

Both Pat and Jack had long and distinguished careers with FDA—Pat joined the agency in 1964, and Jack in 1965. Both had received several awards, including the FDA Commendable Service Award. They both received the FDA Award of Merit in 1989 "for outstanding dedication and personal sacrifice in conducting foreign inspections to assure the safety of fruit exported to the United States."

The dedication of Jack and Pat to the FDA, their community, and their families was unsurpassed. Attesting the recognition of their contributions to the protection and promotion of the public health of the citizens of the United States, more than 600 persons—including Louis W. Sullivan, M.D., Secretary of the Department of Health and Human Services (DHHS); James O. Mason, M.D., Assistant Secretary for Health; Frank E. Young, M.D., Ph. D., Deputy Assistant Secretary for Health/Science and the Environment; James Benson, Acting Commissioner of Food and Drugs; the Honorable Octavio Errazuiz, Republic of Chile Ambassador to the United States; and Senator Paul Sarbanes of Maryland—attended the joint memorial service in their honor. During the service, Dr. Sullivan presented to both wives the Secretary's Recognition Award "for stalwart, stellar service to all of mankind." Also, during the service, Sen. Sarbanes stated, quoting from Paul Volcker, former head of the National Commission on the Public Service:

> *Show me a nation with a mediocre public service and I will show you a mediocre nation. America is not a mediocre nation, and one of the reasons it isn't is because it's been blessed with men like Jack Harty and Pat Pouzar, and women also, who have followed the same high standards and made this a nation of quality and of leadership.*

Ambassador Errazuriz, quoting a Chilean poet, ended his remarks saying, "Life is given to us to look for God, death to find Him, eternity to possess Him. Jack and Pat are with God."

Among the many letters of condolences that were received from friends, colleagues, and dignitaries from around the world was a letter from the President of the United States, George Bush, to Mrs. John Harty and Mrs. Patrick Pouzar. The President's letter read in part, "Your husband(s) ... built a distinguished record of public service. (Their) contributions to the Food and Drug Administration will serve as an inspiration to those who will continue (their) important work."

As a testament to the enduring memory of Jack and Pat in the minds of their FDA colleagues, two permanent memorials have been established. The John F. Harty, Jr. Memorial Library was dedicated on October 16, 1992 in the New England District Office where Jack started his FDA career. The Patrick J. Pouzar Investigator of the Year Award is presented annually to FDA's top field investigator.

—Walter M. Batts

After World War II, considerable food and drug production capacity had been destroyed, not only in Germany, Italy, and Japan, but also in occupied countries such as Belgium, France, the Netherlands, Scandinavian countries, and China. Inferior products from war-torn countries that were trying to rebuild production and exports taxed the inadequate import screening resources of FDA. The agency did not simply reject the substandard goods, but it also provided considerable technical assistance to producers in other countries to help them overcome safety and compliance problems.

The birth of the United Nations and its specialized bodies after World War II set the stage for FDA's participation in activities of the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO). The last half of the twentieth century saw the re-emergence of U.S. international leadership in new forums involved in setting standards for food, drugs, medical devices, and animal health products. FDA officials participated in a wide range of harmonization programs, collaborations with counterparts in other countries, and enforcement efforts at the U.S. border and in foreign production sites, to assure safety of imports.

For food, important events were the establishment in 1956 of the WHO-FAO Joint Expert Committee on Food Additives (JECFA) and in 1962 of the United Nations Food Standards Programme, also known as the Codex Alimentarius Commission. FDA Deputy Commissioner John L. Harvey served as Codex Chairman its first four years, a leadership role reprised in 1999–2004 by Thomas Billy, a senior U.S. food safety official. The creation in 1995 of the World Trade Organization (WTO) reinforced the role of Codex, as a WTO agreement made Codex the reference body for food safety standards. At the century's end, FDA officials were participating in trade negotiations, WTO committee meetings, and even trade disputes on topics like hormones in beef and genetically modified crops. For pharmaceuticals, the key organizations have been WHO and the International Conference for the Harmonization of the Technical Requirements for Pharmaceuticals for Human Use (ICH).

Since the founding of WHO in 1948, U.S. biologics and drug officials have played major roles in the establishment of international standards for vaccines, multi-source drugs, and current good manufacturing practices (GMPs). In 1982, FDA spearheaded the formation of the WHO International Conference of Drug Regulatory Authorities (ICDRA) with an inaugural meeting in Annapolis. ICDRA meets biennially. The ICH has represented a highly successful effort to harmonize requirements for drugs and biologics among the principal producing regions. Informal discussions about the concept between Fernand Sauer of the European Commission and Elaine Esber of FDA—during the 1989 ICDRA in Paris—and then with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) led to this unique regulatory-

industry initiative, launched in 1990. Participants are representatives of FDA, European and Japanese regulatory agencies, and industry associations of Europe, Japan, and the United States. Harmonization of regulatory requirements had been pioneered by the European Community, but would have done little good without participation by U.S. and Japanese authorities and industry.

For animal drugs, USDA and FDA have participated actively in work of the Office International des Epizooties (OIE), an international organization of veterinary officials aimed at achieving protection of animal health. OIE serves as the secretariat for the Veterinary International Cooperation on Harmonization (VICH), launched in 1996. In addition, the Codex Committee on Residues of Veterinary Drugs in Foods is chaired by the Director of the Center for Veterinary Medicine of FDA.

For medical devices, FDA was a founding member of the Global Harmonization Task Force (GHTF). Formed in 1992, GHTF is an international partnership of device regulatory authorities and the regulated industry aimed at achieving harmonization in medical device regulatory practices. When FDA chaired the organization in 1999, it created the website (www.ghtf.org) and drafted the procedures for adopting standards and broadening GHTF beyond the five founders (Australia, Canada, Europe, Japan, and the United States). FDA officials also have been leaders in fledgling medical device harmonization efforts in the WHO and Pan American Health Organization, as well as in voluntary consensus standards for medical devices, on such topics as biomaterials standards and the global quality system standard.

Recognition of FDA as the "gold standard" for product approval decisions probably stems from the agency's refusal to approve the drug thalidomide as a sedative, a watershed event that raised FDA's profile internationally while leading to new laws in the United States, Europe, and other countries to strengthen drug regulation. First marketed in West Germany in 1957, thalidomide sales by 1960 had skyrocketed and the product was also on the market in Great Britain, Canada, Portugal, and other countries. The fact that the product was never marketed in the United States, thanks to the heroic efforts of FDA reviewer Frances Kelsey, raised FDA's international stature as a regulatory body.

At FDA approached its 100th anniversary, the agency had become a model for other countries' national legislation. As noted by journalist Philip Hilts, when President Theodore Roosevelt signed into law the Pure Food and Drugs Act, what was groundbreaking about this legislation on an international level was not the law itself, but the institution that, with its enactment, became the world's foremost consumer protection agency. Hilts writes:

Other nations had long since passed laws to control deceptive and adulterated commerce, but the American law was unique in that it didn't just make nasty business practices illegal [but also] established a scientific agency, a small

body of researchers and inspectors led by the chief chemist, to report on and, in a limited way, police the dark part of commerce in food and drugs.

Thus, the unique contribution FDA has made to the world is the notion of a public health-oriented, science-based, law-enforcement agency. And if broadly speaking, the United States in the late nineteenth century was a net importer of ideas from other countries about how to regulate food and drugs, a century later it clearly had become a net exporter of regulatory ideas, including the very idea of a national food and drug agency.

Several countries—including the Philippines, Thailand, and China—actually have agencies named "FDA." In the early 1990s, FDA helped the Russian government develop pharmaceutical, food safety, and medical device legislation. After the mad cow crisis, FDA was consulted on the drafting of European laws. By the early twenty-first century, all principal national regulatory agencies in Europe, Japan, Canada, and Australia were following the FDA model of regulation of pharmaceuticals, medical devices, and biological products (including tissue and cell products)—although rarely with food—in a single medical product agency.

By the time FDA's second century had begun, the agency's regulatory policies, food safety regulations, drug and medical device premarket reviews, and inspection techniques were viewed widely as the gold standard, and www.fda.gov became a frequently-visited website. FDA's status as a world-renowned consumer protection agency did not happen overnight but was the result of more than a century of international exchange of ideas, information, and expertise with citizens of other countries struggling to solve the same problems that we have faced in the United States.

The remarkable Dr. Wiley, in his 1909 address to the Prince of Wales in Albert Hall, at the International Congress of Applied Chemistry, said:

There are no means of bringing nations to a better understanding of their mutual hopes and endeavors, no better ways of preserving international peace and amity, than by gathering the fruits of science, borne by its application to all industries.... [D]elegates from all countries of the world... have come to be mutually helpful in the work we are trying to do for the benefit of man. Our purpose is to soften, if possible, the hardships of the poor, to lighten, to some extent, the task of labor by making it more fruitful, to prevent sickness and promote health, to prevent crime and punish wrong-doing, and to eliminate from commerce every species of fraud and misrepresentation.