The Road to the Biotech Revolution - Highlights of 100 Years of Biologics Regulation

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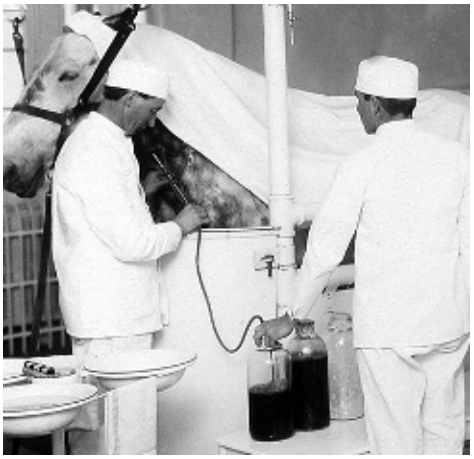
Jim was an ordinary horse, but he had an extraordinary effect on public health. Some say this retired milk wagon horse spurred the passage of the law that eventually gave the Food and Drug Administration its regulatory authority over vaccines and other biological products.



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In 1901, diphtheria patients were routinely treated with antitoxin derived from the blood serum of horses. After 13 children died of tetanus because of contaminated antitoxin, Congress passed the 1902 Biologics Control Act, giving the government its first regulation of vaccine and antitoxin production.

Jim's prominence stemmed from a tragedy in St. Louis in 1901. At that time, the standard treatment for children with diphtheria was an antitoxin serum made from the blood of horses. Jim had produced over 30 quarts of antitoxin in three years, but the horse was destroyed after contracting tetanus. The serum from Jim's tainted blood was accidentally bottled and used to treat diphtheria patients, causing the death of 13 children. The serum had been manufactured in local establishments with no central or uniform controls in place to ensure potency and purity. Nor were there inspections or testing of the final product.

Around the time of the St. Louis deaths, a similar tragedy occurred in Camden, N.J. Nine children died from tetanus after receiving contaminated smallpox vaccine.

Recognizing the critical need for regulatory safeguards, Congress passed the Biologics Control Act in 1902. Also known as the "Virus-Toxin Law," the act gave the government the first control over the processes used to make biological products, or biologics, and the responsibility to ensure their safety for the American public

Biologics include medical products made from living sources, such as humans, animals, plants, and microorganisms. Today, the FDA's Center for Biologics Evaluation and Research (CBER) regulates biologics, such as vaccines, blood and blood components, allergenic patch tests and extracts, human immunodeficiency virus (HIV) and hepatitis tests, gene therapy products, cells and tissues for transplantation, and new treatments for cancers and other serious diseases. The CBER works to ensure the safety, purity, potency, and effectiveness of these products, helping to get treatments on the market for known diseases and to protect against threats of emerging infectious diseases and bioterrorism.

From the Hygienic Laboratory to the CBER

Under the 1902 Biologics Control Act, the CBER's predecessor, the Hygienic Laboratory of the Public Health and Marine Hospital Service, issued regulations mandating that producers be licensed annually for the manufacture and sale of vaccines, serum, and antitoxins. Manufacturing facilities also were required to undergo inspections, and licenses could be revoked or suspended in cases of violations. Labels were required to clearly show the product name and expiration date, and a qualified scientist had to supervise production

In the several decades after the passage of the 1902 act, the Hygienic Laboratory issued licenses to pharmaceutical firms to make smallpox and rabies vaccines, diphtheria and tetanus antitoxins, and various serums to protect against bacterial infections such as scarlet fever.

In 1906, Congress passed the Pure Food and Drugs Act, which outlawed foods and drugs that were mixed with inferior or impure ingredients (adulterated), or that bore false or misleading claims. But the law made no reference to biological products. Under another law passed in 1938, the Federal Food, Drug, and Cosmetic Act (FD&C Act), a biological product was considered to be a drug. Although parts of the 1938 act were applied to biologics, the act did not modify or supersede the provisions of the 1902 Biologics Control Act. After 1938, the appropriate provisions of the 1902 and 1938 acts were used to regulate biologics.

In 1930, the Hygienic Laboratory was renamed the National Institute of Health, which became the National Institutes of Health (NIH) in 1948. Biologics control remained part of the NIH until 1972, when it was transferred to the FDA.

Today, the FD&C Act and another act passed in 1944, the Public Health Service Act, are the principal laws that govern biologics.

Throughout the 20th century, the world witnessed great discoveries in the biological sciences, many of which led to the prevention or eradication of diseases that have devastated populations in the past. For more than 100 years, the CBER has played a prominent role in ensuring the safety and effectiveness of the fruits of these scientific discoveries, including vaccines, blood and plasma products, and cellular and tissue-based products.

Vaccines

Vaccines are among our most important and cost-effective medical interventions, preventing disease in those who receive them and reducing the spread and risk of infections through our communities," says CBER Director Jesse Goodman, M.D., M.P.H.

The predecessors of the CBER reviewed the first vaccines to immunize people against infectious diseases such as polio, whooping cough (pertussis), and rubella, also known as "German measles."

The War on Polio

Infantile paralysis, or polio, was a much-feared disease. Highly contagious, it paralyzed or killed its victims, and children were especially vulnerable.

"When I was 10 years old in 1936, there was a big epidemic of polio in the country and I remember my parents and I lived in an apartment house right across the street from the park," Ruth Kirschstein, M.D., former acting director of the NIH recalled in a 2002 CBER publication, Science and the Regulation of Biologics. "And they would take me to the park every day in the summer and sit me down and say, 'don't talk to anybody, don't go near anybody, don't do anything because you might get polio.' That was the thing people were most scared about and having their children end up in iron lungs."

Former President Franklin D. Roosevelt, who was crippled by the disease, began a "War on Polio" in 1938 with the creation of the National Foundation for Infantile Paralysis, now the March of Dimes. The foundation raised funds for scientists to conduct research on the cause and prevention of polio.

One of these scientists was Jonas Salk, whose polio vaccine gave the country hope for preventing the dread disease. Salk's inactivated, or killed, polio vaccine had to be tested in human trials before the government could license it. By 1954, in one of the largest clinical tests of a drug or vaccine in medical history, 1.8 million children had been inoculated with the vaccine, which was determined to be safe and effective. But later, polio started appearing in vaccinated people. The infection was traced to live polio virus that had survived the inactivation process in two batches of vaccine produced by Cutter Laboratories of Berkeley, Calif. More than 250 cases of polio were attributed to the Cutter vaccine.

In 1955, the U.S. Surgeon General recommended that all polio vaccinations be suspended until the Laboratory of Biologics Control, a CBER predecessor, had thoroughly inspected each manufacturing facility and reviewed the procedures for testing vaccine safety. After more precise testing and stricter standards were employed to ensure the complete inactivation of polio virus, manufacturing resumed.

Pertussis Vaccine

Whooping cough (pertussis) is a highly contagious and potentially deadly respiratory infection. Although the pertussis vaccine had been available since 1915, there were many concerns about its potency. In 1944, Dr. Margaret Pittman, a researcher in the Laboratory of Biologics Control,

developed a method to determine vaccine potency. The method became the industry standard, and manufacturers were then able to make and sell whooping cough vaccine based on potency as well as safety and sterility.

Improvements to the pertussis vaccine continue. In 1996, the CBER licensed the first acellular pertussis vaccine for use in infants and children for the primary series of immunizations. Containing only the parts of the pertussis bacterium thought to be important for immunity, the vaccine protects children against whooping cough while causing fewer side effects than the previously used whole-cell pertussis vaccines. In 2005, the CBER approved a new vaccine for adolescents and adults that provides a single booster immunization against pertussis in combination with tetanus and diphtheria.

German Measles Vaccine

In 1964, a global epidemic of German measles spread to the United States, infecting about 12.5 million people that year. Rubella is a usually mild viral disease that most often affects children and young adults, but it is a very dangerous disease for pregnant women. The virus can be transmitted to the unborn child, resulting in conditions such as blindness, deafness, heart defects, and mental retardation.

In 1966, former CBER Directors Paul D. Parkman, M.D., and Harry M. Meyer Jr., M.D., then working as scientists in the NIH's Division of Biologics Standards, reported that they had developed the first effective experimental vaccine for rubella.

Parkman and Meyer prepared a weakened, live vaccine for human testing and inoculated 34 children. None of the children developed rubella, nor did they transmit the disease to their unvaccinated playmates. "The experimental vaccine we made was shown not to be communicable," Parkman said in Science and the Regulation of Biologics. "In the middle of all of this, the U.S. had the biggest rubella epidemic ever, and there were maybe 20,000 babies with birth defects across the country that resulted from rubella in that epidemic."

Based on the success of the Parkman and Meyer vaccine, the first rubella vaccines were licensed in 1969. These vaccines, and the current vaccine that was approved a decade later, have been strikingly successful in controlling rubella. By 1988, there were only 225 reported cases of rubella in the United States.

Influenza Vaccine

The influenza (flu) pandemic of 1918 caused an estimated 20 million deaths worldwide and killed more Americans than all the wars of the 20th century. Early flu vaccines were not always effective because no accurate test was available to measure their potency. In the 1940s, Bernice Eddy, Ph.D., a scientist in the Division of Biological Control, as the CBER was called then, concentrated on developing the first reliable potency test for flu vaccine so that manufacturers could make a uniform product with the desired effectiveness. The first flu vaccine was licensed in 1945.

The CBER plays a vital role in ensuring that new vaccines can be produced in time to respond to each flu season and for future pandemics. "Influenza vaccine is unique because its active ingredients--the virus strains used to develop the vaccine--change almost every year," says Goodman. "Each year, FDA begins working with manufacturers at the earliest stages of vaccine development, and we continue to assist them throughout the production phase."

Blood and Plasma

CBER research has led to important discoveries to safely collect, prepare, and transfuse blood and blood plasma.

In 1942, during World War II, 28,000 military personnel developed jaundice after receiving an injection of yellow fever vaccine prepared with human blood serum. The Division of Biological Control determined the cause to be a virus in donors' blood serum. Division scientists found that the virus was heat-resistant, but that ultraviolet radiation killed the virus in blood serum and plasma. In 1949, regulations were issued that required human blood plasma and serum to be irradiated.

But some types of jaundice, renamed hepatitis, were still being transmitted through transfusions. "Hepatitis loomed very large," said John Finlayson, Ph.D., in Science and the Regulation of Biologics. The former associate director for science in the CBER's Office of Blood Research and Review recalled, "We had no tests for hepatitis A, no tests for hepatitis B, and of course, hepatitis C had not even been discovered."

In later years, scientists identified both hepatitis B virus and hepatitis C virus as possible contaminants in blood products, leading to the licensing of the first tests to screen blood for these viruses. Today, all blood products are tested for hepatitis B and C to prevent contaminated blood from being used for transfusions or for manufacturing blood products.

Emerging diseases continue to threaten our blood supply. When scientists discovered in 2002 that West Nile Virus (WNV) was transmissible through blood transfusion, the CBER encouraged the development of investigational WNV screening tests. "By partnering with industry and our sister agencies, such as the CDC and NIH, we went from first recognizing the WNV threat to blood safety, to screening for it in the blood supply in just eight months," says Goodman. The new tests were used throughout the country to screen more than 95 percent of the blood supply, intercepting and removing more than 1,000 WNV-positive blood donations before they could be used for transfusion.

AIDS and the Blood Supply

When AIDS emerged with full fury in the 1980s, blood transfusions became suspect. Better screening tests for donated blood were needed, and CBER researchers and the blood and medical product industries responded. In 1985, soon after HIV was identified as the cause of AIDS, the CBER licensed the first test kit to screen donated blood for infection with the virus.

Over the next 20 years, as the CBER licensed improved test kits, the risk of HIV infection from

blood transfusion steadily declined. In 1985, the risk was 1 in 2,500. By the mid-1990s, the risk had decreased to 1 in 500,000. In 2002, it decreased to 1 in 2 million.

Tests that use saliva instead of blood now provide another option for HIV testing. In 2004, the CBER approved a rapid HIV test that uses oral fluid swabbed from the gums to detect HIV-1 antibodies, providing accurate screening results in as little as 20 minutes.

The Biotechnology Revolution in Medicine

The development of new therapeutic proteins and monoclonal antibodies in recent years has advanced nearly all areas of medicine. For example, the mortality rate due to heart attacks, a leading killer of Americans, was substantially reduced by the use of several protein-based agents. These therapies help clear clots from coronary arteries.

Biologic treatments in the form of monoclonal antibodies that selectively target cells on some breast tumors, lymphomas, and leukemias have become valuable cancer therapies. And products that stimulate white blood cell production are decreasing the risk of infections associated with some cancer therapies.

Hormones that regulate red blood cell production now have an important role in the treatment of anemia associated with kidney failure or cancer. Biologic agents that block tumor necrosis factor, a substance involved in immune system responses that lead to joint destruction, have revolutionized the treatment of rheumatoid arthritis. And a protein-based agent helps restore circulation to the brain in people with stroke. Many of these biological products, although originally licensed by the CBER, are now regulated by the FDA's Center for Drug Evaluation and Research.

Skin coverings manufactured from living cells are used on burn victims to thwart bacterial infection until the body can heal itself or healthy skin can be grafted. "These products have dramatically increased patients' quality of life in ways that were previously unheard of," says Goodman.

Challenges for the 21st Century

The CBER's major challenge for the 21st century is to expedite approval of biological products for use by the public while, at the same time, maintaining high levels of safety and quality.

"So many of our products are important for new emerging threats," says Goodman, "especially infectious diseases such as pandemic flu, West Nile Virus, SARS, antibiotic-resistant tuberculosis, and the agent that causes the human form of mad cow disease, variant CJD. There's an incredibly important need for us to be prepared for these threats and to help get products developed rapidly to be able to meet them." The CBER is currently overseeing clinical studies for new vaccines to protect against HIV, hepatitis, WNV, and bird (avian) flu.

"We're no longer just talking about the United States of America," adds Goodman. "Infectious diseases do not respect national boundaries. The world needs to face these emerging threats, and

the world needs to leverage resources to meet them." Drugs and biologics, including vaccines for use in the United States, are increasingly made all over the world, he says. The CBER continues to work with the World Health Organization and other international bodies to foster safety and availability of vaccines, blood, and tissues.

In the past, the CBER's role in regulating vaccines against smallpox helped to eradicate this dread disease. Now, with the potential threat of a biological attack, the CBER's attention is turned once again to smallpox. The CBER's work with manufacturers and the CDC has boosted the national stockpile of investigational smallpox vaccine by hundreds of millions of doses. The CBER is also aiding the development of new-generation anthrax vaccines.

"We need to be ready not only to produce vaccines that can prevent these threats, but to preserve the safety and integrity of blood and blood products," says Goodman. "It's a huge challenge we live with every day." The CBER has taken strong measures to ensure that blood and tissue products continue to be safe, and is helping to produce diagnostic tests to detect bioterrorist agents in blood donations.

The rapidly advancing field of biotechnology presents additional challenges for the CBER. New technologies involving genetically manipulated cells introduced into the body offer the potential to fight disease, restore normal function, repair injuries, replace lost cells, or regenerate failing organs. Stem cell-based treatments could someday repair many different body tissues. And gene therapy products can replace faulty or missing genetic material, potentially treating or curing a disease. The CBER must continue to make sure that these products are as safe as possible while studies of these promising therapies continue.

The study of gene structures (genomics) and proteins in living cells (proteomics) is leading to potentially effective treatments for a variety of serious diseases, including cancer, diabetes, and heart disease. The CBER is collaborating with the NIH on proteomics research that has the potential to provide early diagnosis of disease and early warning of drug toxicity. This work could potentially revolutionize cancer detection and care.

The need for human organs for transplantation far exceeds the supply. Xenotransplantation, the transplant of animal cells, tissues, or organs into a human, offers new hope for an added source of organs. The CBER must advise researchers conducting clinical trials involving xenotransplantation while safeguarding transplant recipients from new infectious agents that animal tissues and organs may harbor.

CBER scientists must continually improve their scientific expertise in order to ensure the safety and effectiveness of new products. "Some products don't fit in the traditional box," says Goodman. "They are not a drug or a biologic or a device. They are oriented toward individual patients or treatment for a rare disease. We are called upon to develop innovative ways to review and to regulate these innovative products."

While keeping pace with cutting-edge science, the CBER must also keep the public informed of new medical products and emerging threats. "It's important to communicate health information and the potential benefits and potential risks of a treatment or product," says Karen Midthun,

M.D., the CBER's deputy director for medicine. "We need to get the public's input and we need to address their concerns," she adds. "We must be able to give them the information they need so they can think through the benefits and risks and make the best choices for themselves and their families."

The Center for Biologics Evaluation and Research (CBER) regulates

- more than 14 million units of blood and blood components transfused each year in the United States
- more than 235 million vaccinations given each year to prevent serious diseases
- more than 1 million human tissues transplanted each year to repair injury, restore function, and improve quality of life
- more than 800 active human trials studying experimental cell, gene, vaccine, or blood products for serious diseases such as AIDS, cancer, diabetes, and heart disease.

Legal Action Against Blood Banks

The first prosecution of a licensed blood bank occurred in 1962. The Division of Biologics Standards, the predecessor to the FDA's Center for Biologics Evaluation and Research (CBER), brought suit against John Calise and the Westchester Blood Bank in New York for altering the expiration dates on blood. Calise pleaded guilty and, in 1964, was convicted on three counts of misbranding, three counts of false labeling, two counts of shipping an unlicensed biological product, and one count of conspiracy. He was placed on probation for five years and was forbidden to take part in the manufacture, distribution, or sale of any biologics, including blood products. Today, the CBER develops and enforces quality standards and regularly inspects blood establishments.

Screening Blood for HIV

The appearance of AIDS in the United States in 1981 threatened the safety of the U.S. blood supply. The human immunodeficiency virus (HIV) that causes AIDS is found in the blood of people with the disease, as well as in the blood of those who have been exposed to the virus but who are not yet ill. HIV was not identified as the cause of AIDS until 1984. In 1985, the CBER licensed the first test kit to screen donated blood for antibodies to HIV-1, the most common type of AIDS. Since then, screening tests for both HIV-1 and HIV-2 have been continually improved. In 1985, the risk of HIV infection from a blood transfusion was 1 in 2,500. In 2002, it was only 1 in 2 million.

Edible Vaccines

The FDA regulates a variety of vaccine types, and is preparing to regulate new products now under study, such as "edible vaccines." Edible vaccines have some advantages over traditional vaccines. They are unable to cause infection, are relatively easy to produce in large quantities, and are stable during storage. Researchers produce edible vaccines by genetically altering the edible parts of plants. Substances that stimulate an immune response (antigens) to rabies have been produced in tomato plants, and antigens to hepatitis and cholera have been produced in

potatoes. Bananas are being investigated as possible vaccine delivery foods because they can be eaten raw and appeal to children.